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DEPARTMENTS OF LABOR, HEALTH AND HUMAN
SERVICES, EDUCATION, AND RELATED AGENCIES
APPROPRIATIONS FOR 1997

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Departments of Labor, Health and Hu...

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BEFORE A

SUBCOMMITTEE OF THE
COMMITTEE ON APPROPRIATIONS
HOUSE OF REPRESENTATIVES
ONE HUNDRED FOURTH CONGRESS
SECOND SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND
HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

JOHN EDWARD PORTER, Illinois, *Chairman*

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NITA M. LOWEY, New York

NOTE: Under Committee Rules, Mr. Livingston, as Chairman of the Full Committee, and Mr. Obey, as Ranking
Minority Member of the Full Committee, are authorized to sit as Members of all Subcommittees.

S. ANTHONY MCCANN, ROBERT L. KNISELY, SUSAN E. QUANTIUS, MICHAEL K. MYERS,
and JOANNE L. ORNDORFF, *Subcommittee Staff*

PART 4
NATIONAL INSTITUTES OF HEALTH



Printed for the use of the Committee on Appropriations

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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1997

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES ONE HUNDRED FOURTH CONGRESS SECOND SESSION

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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RE- LATED AGENCIES APPROPRIATIONS FOR 1997

THURSDAY, APRIL 18, 1996.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. HAROLD VARMUS, M.D., DIRECTOR

DR. RUTH KIRSCHSTEIN, M.D., DEPUTY DIRECTOR

**DR. WENDY BALDWIN, M.D., DEPUTY DIRECTOR FOR EXTRAMURAL
RESEARCH**

**DR. MICHAEL GOTTESMAN, M.D., DEPUTY DIRECTOR FOR INTRA-
MURAL RESEARCH**

ANTHONY ITTEILAG, DEPUTY DIRECTOR FOR MANAGEMENT

**FRANCINE V. LITTLE, DIRECTOR, OFFICE OF FINANCIAL MANAGE-
MENT**

**DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET,
DHHS**

Mr. PORTER. The subcommittee will come to order.

We are pleased to welcome Doctor Harold Varmus and Doctor Ruth Kirschstein and all of their staff at the National Institutes of Health. This begins seven days of hearings on the National Institutes of Health. Doctor Varmus, we're very pleased to see that the President's budget put NIH at a high priority. I also have put NIH at a very high priority. We look forward very much to hearing from you and from your staff. We find this one of the most interesting and exciting aspects of our hearing. We appreciate very much your good testimony. So why don't you proceed in any way you want.

If Mr. Obey should come in, rather than waiting, we will ask him to make a separate statement at that time.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Fine. Thank you. I will begin by introducing the other people at the table. Michael Gottesman, the Deputy Director for Intramural Research, Wendy Baldwin, the Deputy Director for Extramural Research, Mr. Tony Itteilag, who is now the Deputy Director for Administration; you know Doctor Ruth Kirschstein, my Deputy Director; Francine Little, who is the Director of the Office of Financial Management, and the steady Mr. Dennis Williams who accompanies us on behalf of the Department.

OPENING STATEMENT

Mr. Chairman, I am pleased to be here to present the President's budget for fiscal year 1997. I do so at a time of special optimism at the NIH. I would like to review very briefly four reasons why we feel particularly upbeat at the current time.

First, of course, I'm talking about the healthy appropriation we received for fiscal year 1996 as a result your deliberations, the support we've gotten in a bipartisan fashion from the Congress, the administration, and our constituencies. We are particularly grateful for this appropriation, not only because it boosts our resources for this year, but also it allows us to operate throughout 1996 in a way that is not shared by many of our partner agencies that do science and work on behalf of health throughout the Government. The appropriation allows us to maintain our research momentum and to jump start a number of initiatives that we had planned for 1997. We are very grateful for the ability to do that.

ADVANCES IN BIOMEDICAL RESEARCH

The second reason for optimism is the incredible rate of advances in biomedical science at the current time. At recent hearings held on our revitalization bill in the Senate by Senator Kassebaum, many of the Institute directors had a chance to show their wares. I hope you will review some of their testimony, and you will hear again about some of those advances in presentations to be given over the next several days. Just briefly, among the things you will hear about are discoveries of new genes that predispose to a variety of cancers, especially cancers of the breast, kidney, and colon; genes that govern obesity, Alzheimer's Disease, and many other neurological diseases; and goals that have been achieved in the mapping of the genome and sequencing of genomes, including one very special advance that will be announced by Frances Collins next week. You will hear about vaccines that prevent pertussis and Hemophilus influenza type B with a minimum of side effects; you'll hear about the first effective treatment for stroke; you'll hear about the marked efficacy of inhibitors of the viral protease for treatment of HIV infection.

Just to give you some flavor of the rate of progress, I've taken the liberty of making a very brief list of a number of advances that have been published in leading scientific journals and reported in the press just in the last few weeks, in the time between the date our hearing was originally scheduled and today. There's been an announcement of a new function for hemoglobin, a discovery of fundamental importance that may have many clinical applications; the discovery of what appears to be a new mechanism for epilepsy resulting from the discovery of a gene that predisposes individuals to epilepsy and encodes a protein that inhibits enzymes that cut up other proteins; there has been evidence for early detection of Alzheimer's Disease through a combination of neuroimaging and the analysis of the gene Apo-E; there's been a new approach to vaccines for the rotaviruses, a class of viruses that cause devastating diarrheal illness in infants; there are the prospects for novel and earlier immunization procedures based on study of a long-term problem in immunology called tolerance; and there was a recent insight

into aging that results from the identification of a gene that causes very early, accelerated aging and makes a protein which is involved in the unwinding of DNA.

IMPROVED COMMUNICATIONS

The third reason for our optimism comes from improved communication between the NIH and its constituents who do health care and science and with the public at large as well. This is manifest, for example, by the journalism that reports on the discoveries I've just mentioned to you; the development of an NIH Home Page that serves the public interested in health advances as well as our grantees constituents who for example, during the furlough and blizzard, needed information about the grant review processes. As you know, Mr. Chairman, in conjunction with Maryland Public TV, we have had two pilot shows called "Health Week" that present research done by the NIH to the public and could lead to a longer term show that would educate people about our progress. A number of other instruments, such as the Cancer Information Service, the MEDLINE that provides research references to health practitioners and to researchers, and the NIH GenBank that is essential for the genome project, all serve essential functions and have been very, very widely used, as documented by the number of times these resources have been used by our constituents.

INTRA-NIH COLLABORATION

Fourth, the NIH is working with a renewed sense of unity and efficiency. There are many new, improved mechanisms for research coordination, for sharing of resources, and cooperation among institutes. This has been one of the themes of my administration, one that's been assisted by the work of Institute directors, particularly some of the new Institute directors that you will hear from during the course of the next couple of days. We have paid attention to the peer review processes, instituted a number of administrative efficiencies I hope we'll have time to talk about, and made better use of computer services and creation of databases to expedite our research activities.

The health of the biomedical research enterprise which I have tried to convince you of in these brief moments requires a variety of elements that include laboratory research, research that involves patients, technology transfer, training, and development of products of our research into therapeutics and preventive strategies against disease. Among all these, one seems to be in a particularly precarious state, and that is clinical research. There are many well-known reasons for this: the difficulty of recruiting medically trained personnel who have accumulated large debts during their training, the inadequacy of clinical research training programs, the impact of managed care upon revenues received by academic health centers, the impact of managed care on recruitment of patients, the deterioration of physical facilities in some places, and the relatively low success rate for grants that we see among certain groups of clinical investigators.

CLINICAL RESEARCH CENTER

The NIH, under my influence, has taken many steps to try to counter these trends, and I have listed those for you in the written statement. Today, I would like to emphasize only one component of the clinical research enterprise, that is carried out at the NIH in our intramural research program. As you know, Mr. Chairman, the intramural clinical research program that is conducted at the Clinical Center at NIH has been the heart of our intramural program and has been the center for clinical research nationally and, indeed, throughout the world. Roughly half of all federally-funded research hospital days occur there as well as about a quarter of outpatient visits for research purposes throughout the Nation. The Clinical Center has been the place where many clinical investigators across the Nation have received their training, and there are roughly 1,000 active research protocols. We study a very wide range of diseases, including extremely rare diseases that would be difficult to study in any single location that was not nationally mandated. In addition, the Clinical Center provides security for clinical research against the erosion that's felt at academic health centers largely due to the impact of the conflicts in the health care marketplace.

In response to these changes, in conjunction with John Gallin, the new Director of the Clinical Center, we've undertaken a number of initiatives to try to improve matters. We have new training programs for clinical investigators. We have actively recruited clinical investigators and have established a loan repayment program for prospective clinical investigators who come from disadvantaged backgrounds. We are improving the operations of the Clinical Center in response to a report commissioned by the Department of Health and Human Services and led by Helen Smits, the Deputy Administrator of the Health Care Financing Administration by putting in place a new board of governors, stabilizing the funding of the Clinical Center, and streamlining many of its procedures. We have developed new means for outreach to the extramural investigator community to improve sharing of our resources, develop new collaborations, and make the Clinical Center a national resource for clinical investigators everywhere. We have put in place telemedicine procedures and televised our grand rounds. And lastly, as you know, many studies have indicated that the Clinical Center itself is deteriorating. It was opened in 1952, and is no longer a state of the art building. We have proposed to construct a new facility to rectify the physical deficiencies.

BUDGET REQUEST

This brings me to the budget proposal itself. The President is asking for \$12.406 billion for fiscal year 1997. This represents a \$467 million increase, or a 3.9 percent increase. Of that \$467 million, \$310 million would be the allowance for construction of the new hospital which we call the Clinical Research Center (CRC). Nearly all of the rest would be devoted to research project grants to sustain a continued growth of the pool of research grants. In addition, the budget proposal includes a strong recommendation for a consolidated budget for the Office of AIDS Research, as in the

NIH Revitalization Act of 1993, to give the OAR proper control over the research program for that complicated disease.

How does our budget preserve funds for grants despite the fact that a large fraction of the increase would be devoted to the Clinical Research Center? The poster that I hope is visible to you on your right shows, first, the way in which we distributed our increased funds for fiscal year 1996. You will note in particular the reduction that was made in response to this committee's direction to decrease the amount of money for the Research Management and Support category. In addition, the major share of the allocation went to research project grants.

In 1997, with less money available for all these categories, we would hold virtually all categories constant except for research project grants. In addition, we are proposing to pay only a 2 percent rather than the traditional 4 percent increase to our continuing non-competitive awards. This is done for two reasons. First, we've determined that the rate of inflation, the so-called biomedical research and development price index, has been below 4 percent for the last three years. We find that by restricting growth to 2 percent, rather than the traditional 4 percent, we can increase the number of grants to a record total number of 25,400 with roughly 200 more new grants in 1997 than we paid in 1996.

In conclusion, Mr. Chairman, you and I share pride in the NIH and its accomplishments—broadening knowledge, improving health, stimulating the economy, and leading our country to world dominance in medical research. Despite the difficult budgetary times that we're living through, the President's budget will allow us to foster our traditional goals—the support of investigator-initiated research—while also building a necessary facility for patient-oriented research.

I would be pleased to answer any questions that you and your colleagues might have.

Thank you, Mr. Chairman.

[The prepared statement and biography of Dr. Harold Varmus follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Statement of the Director

I am pleased to present to you the President's FY1997 Budget for the National Institutes of Health (NIH). For reasons that I will describe in a moment, this is an unusual budget that will require special attention to its rationale and impact.

Optimism at the NIH

I bring this budget to you at a time of extraordinary optimism and productivity at the NIH. Several explanations for this buoyancy of spirit are at hand:

(1) Despite the budgetary restraints that have been applied to many Federal programs in this fiscal year, the NIH is benefiting from bipartisan support from the Congress, the Administration, and the public. As a result, at a time when we were learning to expect "steady state" budgets, we have received an increase of 5.8 percent for FY96 over FY95. This has allowed us to commence specific new initiatives in the neurosciences, cancer research, the study of connective tissue disorders, and other fields; to pursue the several NIH Areas of Research Emphasis with special vigor, and to support a large number of outstanding research projects that promise to enhance knowledge and improve health.

(2) Advances in laboratory and clinical sciences are occurring with great rapidity. Many of these advances were featured during the NIH authorization hearings recently conducted by the Senate Labor and Human Resources Committee. The Senators learned about a newly discovered hormonal pathway governing appetite and metabolism that was found by isolating mutant genes from obese, diabetic mice and rats; about genes that predispose women to high rates of breast cancer, including one easily detectable mutant gene that is found in as many as one percent of Ashkenazi Jews; about the events governing the death of cells in Parkinson's Disease, Alzheimer's Disease, and other neurological conditions; about the protease inhibitors that have revolutionized the treatment of HIV infection; and about new vaccines for Hemophilus influenza B and pertussis that are protecting children from debilitating illnesses and from the side effects of earlier vaccines. You will hear more about these accomplishments and others in subsequent testimony from the ICD Directors, and you can read more about them in the recorded and submitted testimony from the authorization hearings.

(3) The NIH has greatly expanded its abilities to provide information to its constituents. New means of data storage and communication are improving our services to the research communities, health care providers, and the general public. As the Human Genome Project and other DNA sequencing activities continue to grow rapidly, investigators all over the world have become increasingly dependent on the retrieval and analytic systems in the NIH GenBank.

MEDLINE, the NIH database for articles in medical journals, now contains 8 million references and was consulted 7.5 million times last year. Half of these literature searches were for purposes of patient care in offices and hospitals, in cities and our most rural areas. NIH also operates a frequently visited site on the World Wide Web, the NIH Home Page, with over 25,000 contacts each day; our most popular consumer health booklets will soon be placed on line to increase accessibility. In addition, the Cancer Information Service has handled nearly 7 million calls since it was founded in 1976. To further expand our contact with the public, the NIH recently funded two pilot episodes of Health Week, a Maryland Public Television news show about medical research and its applications.

(4) The NIH is operating with a new sense of unity and with a renewed dedication to efficiency. The conduct of research has been enhanced by several kinds of collaboration, coordinated planning, and sharing of resources. Trans-Institute "special interest groups" have transformed the intramural research program; Institutes are working together to promote the NIH Areas of Research Emphasis; and extramural and intramural facilities are being widely shared. For example, over 600 extramural scientists are using the Frederick Biomedical Supercomputing Center and the number is growing by 30 percent annually. Efficiencies are also apparent in many administrative activities. Most of the ICDs now participate in one or more "competitive service centers" that are conserving dollars and FTEs while providing procurement, grant review, travel, patient recruitment, and other services. New computer resources are being used to develop electronic grant submission, invention reporting, and data bases on trainees and clinical trials. Improved methods for submitting and reviewing grant applications are also saving money at the NIH and at extramural institutions. Finally, a DHHS review of the administration of the NIH Clinical Center, the Smits Report, has proposed several important changes, including creation of a Governing Board, a more predictable budget, and many cost-saving efficiencies in management.

Clinical Research in Transition

A healthy biomedical research enterprise requires financial support, excellent facilities and equipment, and talented personnel for a wide range of activities, from fundamental laboratory research to clinical trials. Only in this way can discoveries in the laboratory be converted to health benefits for our citizens. Yet clinical research, both at the NIH and in the extramural community, is threatened by deteriorating physical facilities, inadequate recruitment and training of patient-oriented investigators, and declining populations of clinical subjects. The increasing dominance of managed care networks, with their emphasis on cost control, further challenges research and teaching activities at the nation's academic health centers, where most NIH-supported clinical investigation is conducted. We need to be prepared to respond to these trends if we wish to sustain the integrity of patient-oriented research programs at a time when advances in genetics and cell biology promise dramatic changes in the practice of medicine.

The NIH is employing several strategies in a campaign to counter the nation-wide erosion of clinical research. (a) We have established a Clinical Research Panel, chaired by Dr. David Nathan of the Dana Farber Cancer Center, to advise the NIH Director on the funding of clinical research, the training of clinical investigators, and the revitalization of the sites at which such

research is done. During the coming year, we expect this Panel to make important policy recommendations that will enhance the vitality of clinical investigation throughout the country. (b) We have developed at the NIH (and encouraged elsewhere) special courses in patient-oriented investigation and loan-repayment programs for training in clinical research. (c) An extramural panel has examined the fate of grant applications to support patient-oriented research and recommended significant changes in the review process. (d) We have surveyed clinical trials supported by the ICDs in order to optimize mechanisms for oversight of the trials. (e) Recently, the National Cancer Institute (NCI) has signed an important agreement with the Department of Defense that will permit members of the armed forces and their dependents to enroll in NCI-supported clinical trials under the CHAMPUS health care system. This could provide a model for reimbursement by other providers and insurers for experimental treatments for many diseases.

The Need for a Renewed NIH Clinical Center

A crucial component of our campaign to enhance the nation's clinical research program is focused specifically on the NIH's intramural activities---improved operations in the existing NIH Clinical Center (CC) and construction of a new facility, the Clinical Research Center (CRC).

Ever since its construction in 1952, the CC has been the core of the Intramural Program, the training site for thousands of the nation's biomedical scientists, and home for the most prestigious clinical research program in the world. The power of this program is intimately linked to the diversity and quality of laboratory sciences present on the NIH campus, especially those practiced in space immediately adjacent to the clinical wards. With nearly half of the country's research beds, a large ambulatory care research unit, a coordinated training program, and over 1000 protocols conducted with patients from throughout the nation and the world, the CC has fostered important work on diseases ranging from the well-known (e.g., cancer and AIDS) to the rare and obscure.

Numerous distinguished review groups, including the Army Corps of Engineers and the External Advisory Panel chaired by Drs. Paul Marks and Gail Cassell, have documented the increasingly dangerous deficiencies in the physical condition of the existing CC and proposed the construction of a new research hospital. In confirming the recommendation for a new facility, the recent Smits Report noted that the efficiencies expected to result from its proposed operational changes can only be fully realized in a building with a modern design. In accord with the advice of the Marks-Cassell Panel, the President's request for NIH will permit construction of a state-of-the-art research hospital with 250 beds, allied clinical facilities, and adjacent research laboratories for work that is closely intertwined with clinical activities, a traditional strength of the existing CC.

Unlike most of the academic health centers at which most extramural clinical studies are conducted, the NIH intramural program is not directly threatened by current dramatic changes in provision of health care that limit recruitment of research subjects and make clinical research programs unaffordable. As a result, clinical research within the NIH intramural program will likely become even more important to the nation than it has been in the past. We are further

augmenting its significance by expanding access to our intramural clinical research resources, including sophisticated technologies and rare patient populations, and by increasing collaborative clinical work with extramural investigators.

The FY 1997 Budget Proposal for the NIH

The budget proposed by the President for FY 1997 would provide \$12.406 billion to the NIH, an increase of \$467 million (or 3.9 percent) over the FY 1996 estimate. The magnitude of this request is determined in part by the allowance of \$310 million in total for construction of the new Clinical Research Center (CRC). In the Administration's budget request, \$11,986 million is intended for program costs, \$193 million (or 1.6%) above the FY 1996 program costs projected for the NIH. This increase is significant in a Federal budget plan that allows no increases for many Agencies and makes reductions in many others.

The FY 1997 Request for NIH once again asks that Congress appropriate all AIDS research funds to the Office of AIDS Research (OAR). A consolidated appropriation is the most appropriate vehicle for making decisions about the allocation of AIDS research funding and helps target research dollars most effectively, minimizing duplication and inefficiencies across the 21 Institutes and Centers that carry out research on HIV and AIDS.

The Timing of the CRC Construction

If we are to have a suitable building in place for clinical research activities at the NIH by the start of the next century, we must proceed now. Fortunately, the NIH has received appropriations in FY 1995 and FY 1996 to support the first two phases of the architectural planning process. All of the funds required---\$310 million---beyond the already-appropriated planning costs are now requested in the FY 1997 budget. The award of full costs in this fiscal year will ensure that construction proceeds in an economically efficient manner, minimizing the long-term impact of the financing of this vital building on NIH's other high priorities, including research grants.

In formulating the budget requests for individual ICDs, research support mechanisms, and scientific programs, several objectives have been followed: (a) to maximize the funds available to the extramural research community, especially through the mechanism of investigator-initiated research project grants (RPGs); (b) to encourage ongoing work and commence new initiatives in several areas of medical research that show particular promise (the NIH Areas of Emphasis); and (c) to limit funding for research management and the intramural research program, in accord with recently-achieved administrative efficiencies. As a result, the most significant increases in research programs are in the categories of RPGs (3.2 percent, including Small Business Innovative Research grants) and training (2.4 percent), while contracts, intramural research, and research management in the aggregate are reduced by 0.32 percent. The increases in research funds are nearly equivalent in the AIDS and non-AIDS components of the budget request. Prioritization of programs, as reflected in the NIH Areas of Scientific Emphasis, account for the minor differences in the increases proposed for the various ICD's.

This budget will permit the NIH to support a record number of RPGs (25,400) in FY 1997 and to award over 200 more new and competing grants than in FY 1996, a year in which the NIH budget was increased by 5.8 percent. We have achieved this reassuring forecast in part by limiting support of contracts, intramural research, and research management support. In addition, the support of continuing awards and the average cost of new awards will be increased by 2 percent in FY 1997, rather than the 4 percent prescribed by our Cost Management Plan. The impact of this change is partially offset by recent indications that the Biomedical Research and Development Price Index (BRDPI) has fallen from 4.3 percent to 3.7 percent. The NIH has judged that the minor modification of the Cost Management Plan will not significantly compromise the research activities of our grantees, while offering major long-term advantages: the support of more grantees and the construction of the CRC.

Reprise

By many measures, the NIH is one of the U.S. Government's crowning achievements, promoting the health, knowledge, economic well-being, and pride of this nation and its citizens. For FY 1997, the Administration has crafted a budget proposal that will continue to foster the traditional goals of the NIH, enhance investigator-initiated research, sustain the intramural research program, and build a much-needed clinical research facility in times of fiscal stress.

I will be pleased to answer any questions the Committee might have.

HAROLD E. VARMUS, M.D.
 Director
 National Institutes of Health

Dr. Harold Varmus was sworn in as the Director of the National Institutes of Health (NIH) on November 23, 1993. Dr. Varmus is the first Nobel Laureate to serve as Director of the NIH. He was previously a professor of microbiology, biochemistry, and biophysics and the American Cancer Society Professor of Molecular Virology at the University of California, San Francisco. He is an internationally recognized authority on retroviruses and the genetic basis of cancer.

Dr. Varmus and his UCSF colleague J. Michael Bishop, M.D., shared a Nobel prize in Physiology or Medicine in 1989 for demonstrating that cancer genes (oncogenes) can arise from normal cellular genes, called proto-oncogenes. His work has assumed special relevance to AIDS, through a focus on biochemical properties of HIV, and to breast cancer, through investigation of mammary tumors in mice. His research activities were supported by grants from the NIH; by his professorship from the American Cancer Society; and by the Melanie Bronfman Award for Breast Cancer. He continues his research through his laboratory in the National Cancer Institute at the National Institutes of Health.

Dr. Varmus served as chairman of the Board of Biology for the National Research Council, an advisor to the Congressional Caucus for Biomedical Research, a member of the Joint Steering Committee for Public Policy of Biomedical Societies, and co-chairman of the New Delegation for Biomedical Research, a coalition of leaders in the biomedical community.

The author or editor of four books and over 300 scientific papers, Dr. Varmus has been elected to the Institute of Medicine, the National Academy of Sciences, and the American Academy of Arts and Sciences. His most recent book, "Genes and the Biology of Cancer," intended for a general audience, was co-authored with Robert Weinberg for the Scientific American Library. In 1986, he chaired the subcommittee of the International Committee on the Taxonomy of Viruses that gave the AIDS virus its name HIV.

Dr. Varmus was born December 18, 1939. He attended public schools in Freeport, Long Island, N.Y. He is a graduate of Amherst College (B.A. 1961), where he majored in English literature; Harvard University (M.A. in English literature, 1962); and Columbia University (M.D. 1966). While at medical school, he worked for three months at a mission hospital in northern India.

After an internship and residency in internal medicine at Columbia-Presbyterian Hospital in New York, Varmus served as clinical associate for two years at the National Institute of Arthritis and Metabolic Diseases at the National Institutes of Health. Dr. Varmus went to UCSF as a postdoctoral fellow in Bishop's laboratory in 1970, initiating a longstanding collaboration to study tumor viruses, and was appointed to the faculty later that year. He became a full professor in 1979 and an American Cancer Society Research Professor in 1984.

CLINICAL RESEARCH CENTER

Mr. PORTER. Doctor Varmus, thank you very much for your excellent testimony. Let me begin by asking you about the clinical center proposal. As you said, the President's budget provides a \$467 million increase for NIH, but \$274 million of that increase is designated for the replacement of the clinical center. Some people in the extramural community would support a new clinical center but they balk at funding it at the expense of research grants. How do you answer critics who think that this is being done, in part at least, at their expense?

Dr. VARMUS. Well, there's no way that we can construct this building without paying for it. So, clearly, any money that's spent on it is money that could be seen as money that would go elsewhere. In fact, as the budget was constructed, the agreement to ask for the money to build this building was an add-on in the budget. That is, I don't believe that the money is being taken away from extramural research. This is a very tight budgetary environment and the money that is being requested is money that is being requested in response to a clear need.

INFLATIONARY GRANT INCREASES

Mr. PORTER. You have said that you're going to increase the number of new extramural grants awarded in the next year rather than provide a full inflation adjustment, although you said that 4 percent is probably higher than the inflation figure has been. But 2 percent is probably too low though also, wouldn't you agree?

Dr. VARMUS. Two percent is lower than the inflationary figure. At the moment, we believe the inflation for biomedical research is going to be about 3.4 percent for FY 1997.

[CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this figure to "3.7 percent" for the record.]

Mr. PORTER. I wonder if we won't find, if this is done, that there is some cost push in this. In other words, the very fact that we've been increasing it at a higher percent might keep the inflation figure higher than it really otherwise is. I would imagine that's what we'll find. But what reaction will there be to a 2-percent adjustment in the extramural community?

Dr. VARMUS. I have been inquiring of my colleagues about this, and I myself have had some experience as an extramural investigator. I don't believe that a 2-percent increase is going to cause significant burdens. It is a one year reduction that we hope to return to previous cost management figures, or something close to the inflationary rate, in 1998. I know from my experience as an investigator that if we know ahead of time what the increase is going to be, as long as there is some increase, I believe that it will be possible for our investigators to adapt to it.

INTRAMURAL RESEARCH

Mr. PORTER. Other than that adjustment, a great deal of your increases of last year would be lost, particularly in intramural research, would they not?

Dr. VARMUS. Well, they wouldn't be lost. It would just mean that—

Mr. PORTER. Be less of an increase.

Dr. VARMUS. We are imposing some extra burdens on the intramural research program. When we were advised by the Marks-Cassell Panel two years ago about the construction of the clinical center, they advised that if we were to build the clinical center, as they recommended that we do, there would be a disproportionate burden on the intramural program, and that will be seen in the coming year. We are concerned about that but we believe that we can make economies in intramural budget that will allow research to proceed at a reasonable pace.

CLINICAL RESEARCH CENTER

Mr. PORTER. If we could find a way within our scorekeeping rules to fund the clinical center in increments over three or four years, which I think is the time necessary to build it, would you prefer that approach in order to lessen the budget impact on research?

Dr. VARMUS. This cuts both ways. The OMB has advised us that funding the building in a single year promotes efficiency and, of course, it also guarantees that we will be able to complete the building because we have all the money in hand. It also allows us to absorb the impact of the cost of the building in a single budgetary year. There are trade-offs, obviously, for the solution you propose, and I would welcome further discussion of it.

Mr. PORTER. Have you pursued the option of seeking private sector contributions for the construction of the clinical center? If so, to what extent?

Dr. VARMUS. We've considered them. We have a business manager, Boston Properties, that is advising us about ways we can try to supplement funds for the construction of the clinical center. We do have an authorized vehicle, the National Foundation for Biomedical Research, that could receive donations that could be put to that purpose. We don't, however, think it's likely, given the fairly small amounts of money that have been forthcoming from private donors in the past, to envision raising a very large amount of money for the Clinical Research Center in that way.

BASIS FOR ALLOCATING FUNDS

Mr. PORTER. As you know, the subcommittee has already heard from public witnesses, many of whom represent specific disease groups. As in previous years, a number of these groups have urged us to increase funding for their disease relative to others based on the dollars currently spent per death or per case identified. As a subcommittee, we have tried to avoid getting embroiled in this dollars per death debate, believing that other criteria are equally relevant. I know that you share our concern on this issue. Can you lay out for us, and feel free to expand for the record, what basis we should use to allocate biomedical research dollars.

Dr. VARMUS. Clearly, Mr. Porter, the magnitude of the impact of illness is a factor to be considered as we put the budget together. But as many of my colleagues, especially Doctor Lenfant, have pointed out to me, budget building by body count is not the right way to go, nor is simple economic impact the right way to go. We have to consider the opportunities for scientific advancement that spreads more widely through our portfolio. We need to consider the

quality of applications that we get in certain categories. We need to recognize that if we simply considered impact on the economy or on mortality figures as a major criterion, we would be spending very little on rare diseases. We know, first of all, that rare diseases are important to those who are afflicted by them; and secondly, that many of the most important discoveries we have made have come from the pursuit of rare diseases. I mentioned just a few moments ago the recent discovery of a gene that is involved in premature aging in a rare disease (Werner's Syndrome). My personal belief is that studying those genes and their protein products is going to be extremely revealing about many components of the aging process, including cancer and other diseases. Unless we adapt our budgeting of the research monies in accord with the scientific priorities as well as the public health impact, we're going to be failing to take advantage of many opportunities that currently exist.

HISTORY OF BUDGET REQUEST

Mr. PORTER. Let me ask the same question I asked last year. Are the figures that were submitted in the President's budget the same figures that NIH submitted to OMB as far as allocations by institute?

Dr. VARMUS. Yes. In the final pass back.

Mr. PORTER. Explain that for me.

Dr. VARMUS. Well, initially, we submitted a budget that was not laid out by institute. When we received figures from the administration that allowed us to shape our budget and a total amount was allocated to the clinical center, then we were given the flexibility to propose a budget both by research mechanism, as shown on the chart, and by institute. The proposal accords with our sense of where research emphasis should be placed and with our view of which research mechanisms should be employed with the money that was available after paying for the Clinical Research Center.

Mr. PORTER. Rather than describing the factors that you employ in making these decisions, could you describe to the subcommittee the process by which you go through to determine allocations by institute.

Dr. VARMUS. This budget is obviously an unusual one because of the cost of the Clinical Research Center. In light of that, I had a series of meetings with all the institute directors and their budget officers to consider the budget that would remain after we deducted the cost of the Clinical Research Center. We considered primarily mechanisms, as shown on the chart, and we also considered the so-called areas of research emphasis that are in the written material that we've submitted. So when we took both of those into consideration, we ended up with allocations across the institutes.

You will notice that—especially in view of the relatively modest increases in those budgets across the institutes—there are no major variations. Some people looking extremely closely at the budget may make a lot of a hundredth of a percent difference between one institute and another. Those, of course, are not the results of any considered ranking of the institutions but only the outcome of this deliberative process.

Mr. PORTER. Thank you, Doctor Varmus. Ms. Pelosi. We're going to operate on the eight minute rule.

Ms. PELOSI. Thank you, Mr. Chairman. Doctor Varmus, welcome. Thank you very much for your great leadership at NIH.

Dr. VARMUS. Thank you, Congresswoman Pelosi.

LEVINE REPORT

Ms. PELOSI. Your friends in San Francisco are all very proud of you, as you well know, and always have been. Dr. Varmus, I wanted to ask you about the Levine report. For the benefit of my colleagues, last month, for those of you who are not aware, the Levine Committee report, an external review of the NIH AIDS Research Program conducted by more than 100 scientists from universities and industry was released. The report makes a number of significant recommendations. First, let me say how courageous it was for you to open the NIH Research Program up to independent and external review. I commend you for that, Dr. Varmus, and ask you what you intend to do about these recommendations.

Dr. VARMUS. As you mentioned, this report makes a number of very significant recommendations. The panelists recognized that we are at a turning point in the study of HIV and AIDS, that we have had some major accomplishments, and that now it is time to re-evaluate where we are and to set off in some new directions. In particular, they recommended that there be more money spent on investigator-initiated activities; that we emphasize a number of components of our research that would be directed toward the production of effective vaccines; that we place more emphasis on prevention; and that we reconstruct of our AIDS clinical trials units, among a number of other recommendations.

All of the institute directors have received this report. They are studying the over-arching summary, which you are familiar with, as well as the reports of the six individual subpanels of the Levine Committee I have begun to meet, along with Dr. Paul, the Director of the OAR, with the directors of the institutes that are principally involved in AIDS research to consider how to carryout the suggestions of the report. Some suggestions are of greater significance than others, some will be easier to implement and implemented more rapidly than others, and because some involve very fundamental changes in the structure of our programs that can only be achieved over several years. I expect to have at least an outline of how we will be proceeding by the time that my advisory committee meets in June and by the time the OAR advisory committee meets within the next few months. That will give us at least an outline of how we proceed, but I believe that the Levine Report is of such depth that we will be responding to it for the next eighteen months to two years.

OFFICE OF AIDS RESEARCH

Ms. PELOSI. I look forward to hearing more about how you follow up on that. The Levine Committee also unanimously recommends an even stronger role for the Office of AIDS Research. As you know, it says the OAR budget authority for all intra- and extra-mural AIDS research mandated by the NIH Revitalization Act of

1993 must be preserved and it goes on to elaborate on that point. Do you agree with this assessment?

Dr. VARMUS. Yes. As you know, Ms. Pelosi, we have asked that the money for AIDS research be appropriated in a consolidated fashion to the OAR in accord with the OAR plan.

Ms. PELOSI. It is also my understanding that in the negotiations for the 1996 omnibus appropriations bill that the White House is asking that the consolidated OAR be restored for 1996. I hope this will happen. In your view, in what ways would restoring the ground rules on the authority for the OAR now rather than later, be of assistance to AIDS research?

Dr. VARMUS. Ms. Pelosi, as you know, we support the consolidated OAR budget; we stand behind the President on that. The money that's been received from this year's appropriation bill of course has been distributed to the institutes.

CHILD ABUSE RESEARCH

Ms. PELOSI. I wanted to ask in another vein about child abuse research. I was so pleased that in one of the President's speeches to the Congress when he was talking about health care that he included violence as one of many of its manifestations. The question I have is about child abuse and neglect. It is amazing to me, I don't know what world I lived in that this is all such a revelation the volume and the kinds of child abuse and neglect that we're being made aware of these days. What is the current status of research on child abuse and neglect at the NIH? Which institutes are funding the research?

Dr. VARMUS. Principally, the Institute of Mental Health and the National Institute of Child Health and Human Development. There are as well some grants in other institutes, and you could get a more detailed description of the activities of those institutes when those institute directors present to you.

Ms. PELOSI. I'll look forward to that. Could you just tell me what the size of the research portfolio is on this subject?

Dr. VARMUS. I don't know the number precisely. We will have to provide that for the record.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH RESEARCH ON CHILD ABUSE

Child abuse is a personal trauma and a national tragedy. For the large numbers of children who experience physical, sexual and psychological abuse, its severe and lasting adverse effects can be felt well into adulthood. Increased rates of dysthymia (mild chronic depression), major depression, suicidal ideation, and suicide attempts are the most common long-term mental health consequences in adults with histories of childhood sexual abuse. NIH research is seeking both a better understanding of the consequences of child abuse and how to treat or ameliorate them, and new knowledge about normal parent-child relationships as a means of developing ways to prevent child abuse and neglect.

Most child abuse research at NIH is being conducted or supported by the NIMH and the NICHD. Largely, NIMH focuses its research on the adverse mental health consequences of child abuse, while NICHD's research in this area is aimed at the antecedents of child abuse, particularly parent-child interactions.

NATIONAL INSTITUTE OF MENTAL HEALTH

NIMH supports studies relevant to the mental health aspects of child abuse and neglect, and research on the availability, quality, cost, use, structure, and effectiveness of mental health services for children, adolescents, and adults. These include studies of: the incidence and prevalence of child abuse and neglect; the identification and assessment of the impact of risk factors for abuse and neglect; the characterization of the development of short- and long-term mental, behavioral, and physical health problems resulting from child abuse and neglect; treatment of victims and perpetrators of abuse and neglect; prevention of child abuse and neglect; factors influencing the availability, provision and use of mental health services in populations at high risk for mental health problems; the assessment of need for and access to mental health services in high risk populations; short- and long-term mental health consequences of intervention approaches.

In spite of extensive psychological and psychiatric studies of childhood sexual abuse, little is known about its biological manifestations and consequences. Knowing that stress produces fear and anxiety, and increases activity in specific brain regions that regulate memory, and emotion, NIMH-supported researchers examined this functional activity in sexually abused girls. The findings of this study of girls 8-15 years old are consistent with findings from animal studies that have demonstrated a long-term dysregulation of the stress coping system after early trauma. These animals often appear normal until they are stressed, then a functional disorder emerges.

Although it is clear that far too many children experience trauma, its psychological impact has been unclear. Thus, NIMH-funded researchers studied the prevalence of trauma (including child abuse) and posttraumatic stress disorder and their impact on the psychosocial functioning of 384 older adolescents in a community setting. Nearly 15 percent of those suffering a trauma developed posttraumatic stress disorder (PTSD) and demonstrated widespread psychosocial impairment by age 18. Compared with their peers, these youths were at the greatest disadvantage in almost all developmental tasks of late adolescence. They displayed clinical levels of both internalizing and externalizing behavior problems, performed poorly in school, had higher rates of

suicidal ideation and attempts, had more interpersonal problems and somatic complaints, and had an increased risk for additional psychiatric disorders. Youth who had experienced trauma but who did not develop PTSD also showed deficits in many of these same areas when compared with their peers. These findings send a clear message to clinicians to offer prompt clinical aid to young people who have suffered a violent or traumatic event.

NIMH is participating in a Request for Applications (RFA) "OD-96-002--Research on Violence Against Women and Violence Within the Family." The NIH Office of Behavioral and Social Sciences Research (OBSSR) recently announced this special RFA that especially encourages research on the abuse of children and elderly people, partner violence, sexual violence, and perpetrators and victims of multiple episodes of family violence (for example, abused children who witness parental domestic violence). Coordinated by OBSSR, this inter-departmental and trans-NIH program is co-sponsored also by the NIH Office of Research on Women's Health (ORWH), the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Aging (NIA), the National Institute of Justice (NIJ), the National Center on Child Abuse and Neglect (NCCAN), and the Centers for Disease Control and Prevention (CDC). It is intended to bring together perspectives of the participating agencies, encompassing criminal justice, mental health, public health and prevention, alcohol and drug abuse, and child development, to advance our knowledge of family violence and violence against women.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

NICHHD conducts and supports research and research training on biological and behavioral aspects of human development from conception through maturity. One of the main goals of the Institute is to ensure through research the opportunity for each infant to reach adulthood unimpaired by physical, mental or emotional handicap and to achieve his or her full potential.

Most of the research supported by NICHHD that is relevant to child abuse is concerned with parent-child interactions and antecedents of abuse and not child abuse specifically. Currently, the Institute is supporting only two studies which are directly focused on child abuse. One of these examines the interaction of parents and children in families identified at high risk for maltreating the children, and the other focuses on the effect of domestic violence on children's testimony about child abuse and neglect.

The majority of the Institute's relevant research looks at children's relationships with their parents. Some of this research is focused on the role of the social environment in shaping positive social and emotional development. One of the primary social relationships studied is that between the infant and his or her mother. Many investigators are interested in determining the links between child-rearing conditions (for example, the sensitivity and responsiveness of the mother) and the extent to which infants form secure attachments to their mothers. Investigators are also interested in the relationship between the infant's attachment to the mother and his/her later social development. NICHHD is supporting a number of research groups who are studying the rearing conditions at home and in child care that affect infant attachment and the relationship between infant attachment and the social-emotional outcome of the same children when they are toddlers

and preschoolers. The social-emotional development of the children is assessed in terms of compliance, mother-child interaction, peer interaction, and behavioral problems.

Cross-cultural studies comprise an important component of the research on social relationships. Here, in addition to studying mother-child interaction patterns, a major emphasis is placed on understanding how children's social, emotional and cognitive development is shaped by the larger social and cultural network in which they grow up, as well as how children with different temperaments and histories might be differentially affected by specific types of social environments, child-rearing practices, and types of experiences.

SUPPORT FOR RESEARCH ON CHILD ABUSE AND NEGLECT

(Dollars in Thousands)

	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
NICHD	\$19,641	\$20,500	\$20,800
NIMH	10,081	10,000	10,000
NIDA	1,674	1,750	1,800
NIAAA	712	800	825
NINR	674	674	674
<i>TOTAL</i>	32,782	33,724	34,099

Ms. PELOSI. So what other institutes would have——

Dr. VARMUS. Mainly those two Mental Health and Child Health and Human Development, but no doubt there are smaller allocations in some of the other institutes. It is sometimes difficult for us to give you all the information about a topic that may not be used as a cataloguing principle. Of course, a grant that addresses child abuse may well involve other things. So until we look at the numbers carefully, it is difficult for us to give you the accurate number I know you would like to have.

B-START

Ms. PELOSI. Okay. I am very pleased to learn that the National Institute of Drug Abuse has recently announced that it will implement a behavioral science research program named B-START, Behavioral Science Track Award for Rapid Transition. This program has already proven to be a terrific success at the National Institute of Mental Health. I am particularly pleased that NIH is responding to the recommendations by the National Research Council to increase the training opportunities for behavioral sciences. Would you recommend that other NIH institutes look to this program as a model that could be replicated? You may not be aware, but Chairman Porter and the ranking member Mr. Obey and I and others circulated a letter to the House of Representatives regarding last year's basic behavioral science research for mental health. In any event, I just wondered if, getting back to my original point, if the B-START model was one that you would see any value in replicating.

Dr. VARMUS. Frankly, Ms. Pelosi, I'm not sufficiently familiar with the details of the program to make a comment at this time. What I would like to be able to do is to work with Dr. Norman Andersen who is now the Director of our new Office on Behavioral and Social Sciences and get back to you on that.

[The information follows:]

BEHAVIORAL SCIENCE TRACK AWARD FOR RAPID TRANSITION (B/START)

The Behavioral Science Track Award for Rapid Transition (B/START) was initiated in FY 1993 by the National Institute of Mental Health (NIMH) as a way to facilitate the entry of new investigators into the field of behavioral science research. The National Institute of Drug Abuse (NIDA) has now also adopted the B/START program. The program is of special interest to NIDA because the understanding of basic behavioral processes is fundamental to curbing drug abuse and addiction. It is designed to provide one year of funding not to exceed \$50,000 in direct costs for independent investigators (i.e. post-training) who have not previously been principal investigator on any PHS-supported research grant. The funding mechanism used to support this initiative is the small grant (R03).

The Office of Behavioral and Social Sciences Research (OBSSR), which is charged with facilitating and coordinating behavioral research across NIH, is pleased that both NIMH and NIDA are using this mechanism to facilitate the entry of new behavioral scientists into research careers. The OBSSR is currently forming a task group to examine behavioral science training efforts at all NIH institutes and centers. This task group will identify the best and most effective training mechanisms for behavioral and social scientists (including B/START) and determine which are best suited for replication across NIH.

FUNDING FOR NEW AIDS DRUG THERAPIES

Ms. PELOSI. Thank you. In closing, I just want to again publicly commend our Chairman for putting in the \$52 million for the AIDS

Drug Assistance Program money for the new drug therapies. You alluded to them in your remarks and I would hope that we would have an appropriate request for 1997 that attempts to meet the need. Thank you very much. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi. Mr. Bonilla.

Mr. BONILLA. Thank you, Chairman. Dr. Varmus, I would like to start by complimenting you on what you're doing at the NIH. You've been a real plus for the institutes as well as your fine group of researchers and doctors that have been with you from the beginning. It is also nice to see the effort to let the public know what you're doing. I've seen Dr. Fauci on television on many occasions speaking very well about developments in AIDS research. So hats off to you for doing a good job.

Dr. VARMUS. Thank you, Congressman.

INDIRECT COSTS

Mr. BONILLA. I would like to begin by talking about indirect costs, Dr. Varmus. We're all interested in providing you what you need at NIH, but in the event that it gets down to the priorities, we want to possibly look at some areas where we can have some additional savings to provide more research money. Tell me what you think about trying to put caps on indirect costs? Perhaps now or providing for the record, if we did a total cap of 70 percent or 65 percent or 60 percent, how much money could that save, and are you supportive of that?

Dr. VARMUS. I'm a little hesitant about it. First of all, I think we have to acknowledge that the money that's spent on so-called indirect costs is actually being spent on research. Research requires administration and facilities as well as it does the actual execution of projects. So we need to be cautious about assuming that what are often called "indirect costs" is somehow not involved in research. Secondly, as you know, we do have a cap on administrative costs at 24 percent. [CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this figure to "26 percent" for the record.] The expenditures in the administrative category have actually gone down to about 23 percent [CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this figure to "26 percent" for the record.] with time and may go yet lower.

The facilities costs are the costs that have risen over the years, although they have been stable for the last several years. We recognize that there is major variation among institutions with respect to facilities costs, depending upon which climate they're in, depending on whether they're State institutions, depending on the intensity of the building programs. We have been looking very intensively, along with other agencies that pay facilities costs, to determine what it is that results in the rates that we're currently paying. If we were to cap indirect costs say at 65 percent, the amount of savings overall would be relatively small. We estimate somewhere in the general ballpark of \$40 million out of the roughly \$2.5 billion that we spend on facilities plus administrative costs. Moreover, those reductions would affect some of our most effective organizations, some of the private, research-intensive universities, and would hit them fairly hard. Until we know what the benefit would be of a fairly small savings, and we learn more about what the im-

fact would be, and learn more about whether there is anything that can be criticized with respect to the way those rates are determined, I would be hesitant to institute that kind of cap.

Mr. BONILLA. You referred to the \$40 million savings. I would appreciate if you would provide for the record what it would save if we capped it at 70 percent, 65 percent, because I think you said at 60 percent——

Dr. VARMUS. At 65 percent. And that's a very rough number, Mr. Bonilla. We have heard about your interest in this matter and we've tried to come up in a very short time with some rough number. But I wanted to give you some sense of where we are, that we would not be talking about a major impact on the overall amount of money being spent on facilities costs.

PHOENIX PLAN

Mr. BONILLA. Could you briefly describe to the subcommittee the Phoenix Plan. My understanding is that it shifts from a cost-based to a price-based system using the health care industry as a model. Tell me what you think of that.

Dr. VARMUS. The Phoenix Plan was developed by a number of university financial officers at a meeting in Phoenix. It does not have the universal approval of the university community. It is being looked at now by the American Association of Universities. It has some recommendations that many of us I think would agree with, such as a very gradual institution of any changes and a rational approach to rate determination. But I believe some of these recommendations would be part of any recommendation that came from the Government. We are expecting that there will be a recommendation made through a proposal to revise Circular A-21 sometime in the next several months. We hope that many of these will be in accord with the views of university administrators.

Mr. BONILLA. If you could think of other ways to suggest savings so that we can get more money directly into biomedical research, I would be interested to hear them. If you would provide them for the record, I would appreciate that.

[The information follows:]

IDENTIFICATION OF COST SAVINGS

NIH will continue to pursue initiatives aimed at reducing the administrative burden for both NIH staff and grant recipients. To the extent that an administrative activity can be reduced (or eliminated) it allows the NIH and recipient institutions to redirect funds into the direct support of research. Objectives under this goal include improving availability and accuracy of information, improving accessibility and responsiveness of NIH staff, and shortening the time from receipt of an application to issuance of an award. We will seek to achieve these objectives through the identification of specific initiatives that will include utilizing "just-in-time" concepts, as well as electronic commerce for the sharing and exchanging of grant information.

Dr. VARMUS. There are some that we've looked at through our own streamlining plans. Just to give you one simple example, we have been using on a trial basis, and hope soon to use much more extensively, a procedure called Just-in-Time, by which those who apply for NIH grants can defer until an award seems likely the submission of forms governing a large number of regulatory issues. This has the potential for saving considerable amounts of money

both at the NIH and at institutions with respect to the costs of preparing these forms.

Mr. BONILLA. So it is just time consuming and costly to prepare them when they may not even be——

Dr. VARMUS. As you know, 75 percent of our applicants don't succeed.

RESEARCH FUNDING PER DEATH FOR SELECTED DISEASES

Mr. BONILLA. I am going to ask, as I have in past years, if you could provide me for fiscal year 1995 how much the Department of Health and Human Services spent on research funding per death for each of the following diseases: Cancer, diabetes, heart disease, HIV/AIDS, and stroke. You may have those numbers readily available, but, if not, provide them for the record.

Dr. VARMUS. We can provide them for the record with the caution that this is not necessarily the best way to think about how we should be spending our money. As you know, there are many diseases that don't eventuate in death but nevertheless cause tremendous suffering.

[The information follows:]

RESEARCH SPENDING PER DEATH FOR SELECTED DISEASES

The NIH research funding per death for HIV/AIDS, diabetes, cancer, heart disease, and stroke is based on the National Center for Health Statistics Provisional Vital Statistics Data as of October 1995.

RESEARCH SPENDING PER DEATH FOR SELECTED DISEASES

[Dollars in thousands]

	FY 1994 spending	Number of deaths—(1994)	Total per death
HIV/AIDS	\$1,299,145	41,930	\$30,984
Diabetes	293,615	55,390	5,301
Cancer ¹	2,345,666	538,860	4,353
Heart disease	775,674	734,090	1,057
Stroke	112,377	154,350	728

¹ Excludes NCI HIV/AIDS cancer funding.

Mr. BONILLA. I understand. I think when I asked for the record last year you said the same thing. [Laughter.]

DIVERSITY DIGEST

Finally, I just have a couple of minutes remaining, I want to read an item from a local newspaper, the Washington Times, and ask for your comment. This was earlier this month. The headline says "Bring Your Other." The NIH says it is no longer healthy, in fact it is offensive, to use exclusive terms such as husband or wife in the workplace. NIH Office of Equal Opportunity publishes what it calls Diversity Digest and the most recent cover story is headlined "Towards Greater Inclusion in the Workplace. When coworkers discuss their spouses, the use of terms such as husband or wife may be too exclusive. If coworkers use the more inclusive terms such as partner, domestic partner, or significant other, more people will feel part of the conversation. If husbands and wives are invited to a work-related social function such as a picnic or a retirement party, the partners of gay employees should be included and made

to feel welcome by the host using inclusive language on invitations and flyers."

I'm just curious to know, Dr. Varmus, do you have a wife, a partner, or a domestic partner, or significant other?

Dr. VARMUS. I have all four. [Laughter.]

Mr. BONILLA. As you can imagine, all of these things kind of catch our attention on this committee when they refer to NIH. I'm going to read one more, "Any Difference Will Do." This is from earlier this week out of the same newspaper. "Respecting diversity is the theme the National Institutes of Health Office of Equal Opportunity has adopted for its NIH workplace diversity initiative. In keeping with the theme, the NIH has published for its employees a list of 50 ways to respect diversity and positively impact the work environment." I'm going to pick a few here. "Start interacting with someone who is different from you; add extra meaning to brownbag meetings by adopting a food theme such as a vegetarian, kosher, or ethnic cuisines." I hope you include Mexican food in that. "Do not laugh or participate in jokes that bash others or reinforce stereotypes, even lawyers have become more sensitive about being the butt of jokes that demean." [Laughter.]

"Develop a technique to let persons know when you hear them refer to women as 'girls' or when you hear a team of men and women referred to as 'you guys.' On an individual level, ask co-workers whether they prefer to be called Native American or Indian, Black or African-American, Hispanic or Latino, hard of hearing or hearing impaired, and people of color or minority. Acknowledge that bias exists as a subtle human characteristic that causes us to make assumptions about others." And one more point is, "attend cultural awareness seminars and discuss what you learned with others. Do this on your own time as well as work time." Just for the record, I would like to be called an American of Mexican descent, if you ever wondered about that.

I have just a question about this. Is a person's work performance review, Dr. Varmus, in any way tied to some of these 50 items that I only chose a few to read to you? Is this part of an official policy or how is this included in NIH policy?

Dr. VARMUS. The articles you are citing, Mr. Bonilla, come from a Diversity Digest and represent the views of the authors. NIH of course is concerned that people in our workplace have adequate respect and that we acknowledge and respect people's origins and cultural beliefs and sexual preferences. So these issues are serious issues, I know my friends at the Washington Times have chosen to make light of them, but we do ask our supervisors to show sensitivity to issues of diversity and to show interest in promoting diversity in the workplace.

Mr. BONILLA. Do you know how much money you spend on this? Is it a pittance amount or is it a significant amount?

Dr. VARMUS. A very small amount. And I must say that the journal does include many informational items that are of broad use to folks in our working environment. I believe it deserves support.

Mr. BONILLA. How are these suggestions going to be implemented? Is it going to be voluntary or what?

Dr. VARMUS. These were the opinions of individuals and don't represent official policy except insofar as they reflect the belief,

which we would all adhere to, that individuals deserve respect and shouldn't feel excluded.

Mr. BONILLA. I think the Chairman is signalling to me that my time has expired. Thank you, Dr. Varmus.

Mr. PORTER. I would like to be known as the American of English-German-Irish-French descent. [Laughter.]

Mr. BONILLA. You're extremely diverse.

Mr. PORTER. The gentleman of Danish descent from Maryland.

Mr. HOYER. When I hear about all this I tell my Irish friends, my father was born in Copenhagen, that my ancestors raped and pillaged through Ireland with impunity so that I was sure they had some Danish blood and I had some Irish blood. Who knows what we all are but I think we're all Americans. I think that's the important thing, and we ought to be treated with respect for that reason if for no other reason.

REORGANIZATIONS

Doctor, I had the opportunity of meeting with Dr. Klausner the other day and we talked about the reorganization that has occurred within his institute. I am wondering what are your views on that and are we doing that in other institutes as well as simplification of managerial structure?

Dr. VARMUS. Yes, we are. There have been very significant changes in the organization in several of the large institutes as well changes as in the work responsibilities—for example, for deputy directors—at some other institutes that are smaller. There has been increasing emphasis on trying to increase the ratio of the supervised to supervisors and to save money as much as possible. That, of course, occurs in part in response to your directive last year to reduce our research management and support functions.

Mr. HOYER. I was interested to hear Dr. Klausner and what he thought his success was.

Dr. VARMUS. The extent of the structural changes there were particularly profound because in the past the Cancer Institute had both intramural and extramural components within the same divisions. Sorting those out I believe has been extremely beneficial to the function of the NCI.

RECRUITMENT OF AMERICAN SCIENTISTS INTO CLINICAL RESEARCH

Mr. HOYER. Doctor, I've heard from a number of young clinical scientists that it has become virtually impossible to recruit American scientists into this field because they feel they are unlikely to have their grants funded. That is something we've talked about for a long time as we've seen the pay line decrease. Can you comment on that and where do you think we are?

Dr. VARMUS. The statement, of course, is an exaggeration. We are recruiting American scientists to clinical research. Clinical research does get funded. We had a study carried out two years ago under the direction of Gordon Williams from Harvard University to ask about the peer review process for patient-oriented research. His study showed that applications to do patient-oriented research appeared to fare especially badly when those applications were being reviewed in study sections with less than 30 percent of their applications in the patient-oriented research category. We're taking

pains to be sure that applications to do such research are reviewed by study sections that are competent and have adequate experience in this area.

I do think that we have a problem with recruitment of clinical investigators that is based on a number of issues. One is the extremely large debt burden that's carried by medical students who may accumulate as much as \$60,000 or \$100,000 in debt before they're finished. Under those circumstances, of course, the incentives to enter practice and try to pay off the debt is very large. So we are enthusiastic about loan repayment programs for clinical research. We have one at the NIH Clinical Center. There are currently 19 individuals from disadvantaged backgrounds who are participating in that program.

The second issue is one of developing training programs that are appropriate for clinical investigation. It has been my own bias that medical schools in general offer two views of the future: one is a research life in laboratories, the other is actual practice. But there is something in between and it is a very difficult and specialized endeavor in which a number of regulatory and operational issues are required. This is clinical research and clinical trials which require a special kind of education. We have developed a course at the NIH Clinical Center under the direction of John Gallin to teach people how to do clinical research. That kind of teaching program has also been initiated at a number of academic health centers, including Duke and Johns Hopkins and some others. We need to spread these kinds of educational endeavors much more broadly. We're trying to do that in conjunction with our extramural partners.

Mr. HOYER. When you said it was overstated because I used the words "virtually impossible" and clearly that's not the case. Maybe you said this and I didn't hear it, but during the 1980s as we saw the pay lines coming down, Joe Early and others—and it's a shame you didn't get to serve during the term of Joe Early. He was an extraordinary member of this committee and did an extraordinary job for NIH and for the health of America. But the concern was that as young people were talking about going into a profession with the expectation of perhaps large debt, that if they felt that there was not a viable context of the research area over the long term that they would be dissuaded from choosing the clinical research option. You say that we are doing it and the debt is one of the questions. But are we at risk, do you think, of losing our premier position in terms of research internationally?

Dr. VARMUS. I think we're at risk. As I mentioned in my opening remarks, I feel these are among the most serious threats to the integrity of our medical research enterprise and that's why we've been devoting so much energy to try to rectify things.

Mr. HOYER. Thank you, Doctor. I am always impressed to see the talent and the commitment that's arrayed both at this table and behind you. When I think to myself what all of you could be making in the private sector if you applied your talents and brilliance in the private sector, if we were paying for the value that we have in this room, the NIH budget would be very substantially higher. It's always a privilege to be here with all of you.

Dr. VARMUS. Thank you.

Mr. PORTER. Thank you, Mr. Hoyer. Mr. Istook.

EEO POLICY

Mr. ISTOOK. Thank you, Mr. Chairman. Dr. Varmus, before asking what I intended to ask, I want to follow up on a couple of things Mr. Bonilla brought up. I am disturbed by a particular part of what he read that came from the NIH Office of Equal Opportunity, presuming that the quote is accurate. That is the particular part where it says "When coworkers discuss their spouses, the use of terms such as 'husband' or 'wife' may be too exclusive", and then they go on to talk about some people may feel more comfortable if you call them significant other or domestic partner. I understand some people may be more comfortable, but if this is accurate, Dr. Varmus, this is the NIH EEOC office telling people they should not call their husband their husband or their wife their wife. If someone chooses to refer to another person as a domestic partner or significant other, that's their business. But when NIH is telling its employees you should not refer to your spouse as a husband or wife, that is wrong and that is warped and that is intolerant. I would like to see you do whatever it takes, and tell us, to eliminate that effort to censor the speech of ordinary people who simply use the term husband or wife. I don't want one penny of Federal money going to try to tell people it is wrong to call their spouse their husband or their wife. I would like to know what else this office may be doing if that's the type of thing they're putting out.

Dr. VARMUS. Mr. Istook, I would just point out that this was not official NIH policy. It was an article written by an individual. In my view, if you read the article in its entirety, it does make a useful point, and that is that if you were the supervisor, for example—

Mr. ISTOOK. I understand the point. I understand their point of saying some people have some different arrangement that you should not be condemning them for. I'm not taking issue with that point. But they go beyond that. They say that you should not use normal references to your wife as your wife because they would be offended. So you have to understand and not be offended by what they say, but they can then be offended by what you say. That is not a proper standard.

Dr. VARMUS. I use the term "wife" with impunity. I believe that everybody on campus does. It is a matter of circumstance. If I were going to invite members of my laboratory to a party and I asked them to bring their companions, I would not say please bring your wife—that would be offensive to female members of my laboratory.

Mr. ISTOOK. But that's your choice.

Dr. VARMUS. I think that is actually the intent of the article. The article was written not by an employee of the EEO office but by someone else at NIH. It was not an editorial. It was not intended to be a declaration of policy. If that were not the last issue of the Diversity Digest, which it happens to have been, it might well have been countered by a series of letters. We have a number of publications on campus where people air their views and the views are responded to. I don't think anybody takes it as a dictum that needs to be followed in ordinary conversation.

Mr. ISTOOK. I wonder about the editorial decisions then. But, unfortunately, we find that too many people that say they desire to be tolerant and promote tolerance and diversity; instead, what they do under the pretense of being tolerant is become intolerant to ways that people are accustomed to conducting their own affairs. I felt the need to bring that up because that part of it I think Mr. Bonilla was right to bring it up.

INDIRECT COSTS

I also wanted to ask a question in follow up to the indirect cost. Is there a correlation between the quality of the research that's done with the grants that you make and the percentage that's assessed or the grant for administrative or indirect cost? Do you find any ratio or any rule of thumb where you say people that charge more or less for administrative or indirect cost generally have a higher or lower quality of work that they perform?

Dr. VARMUS. There's no relationship as simple as that, Mr. Istook, but there is certainly a tendency for some of those institutions that have among the highest indirect cost rates to be the most research intensive organizations. For example, private universities such as Harvard, Cal Tech, MIT, and others, where we know a tremendous amount of very high quality research is done, do have some of the higher indirect cost rates.

Mr. ISTOOK. Is that due to the quality of the research they do or to the cost of living differentials in the areas in which they're located?

Dr. VARMUS. I think it has to do with the fact that they are not State schools and with some of the properties of the climates that require higher costs for utilities. It also has to do with something we don't understand very well that is sometimes referred to as "research intensity", reflecting the amount of money that's being spent in the buildings where such high powered research is being done. One of our trans-agency efforts in the last year has been to try to understand what it is that accounts for some of the higher facilities costs at some of these institutions. We believe that only when we understand that can we begin to make a more rational process of rate determination.

Mr. ISTOOK. Do you start with the question of what are the published cost-of-living differentials in those areas and then see if that alone seems to match up with that or if there is an indication there are other factors at work?

Dr. VARMUS. We certainly look at the cost of construction in those areas, that is an issue. The area in which the rates have increased most are for so-called use allowances or depreciation. Those, of course, reflect the construction of new buildings for research. So the cost of construction costs in the area which I believe are reflections of cost of living would certainly be taken into consideration. We're interested in trying to develop some benchmarks for how those rates might be determined in a way that would be more equitable among the institutions. We are looking at that in conjunction with the Office of Management and Budget, Office of Science and Technology Policy and other agencies.

Mr. ISTOOK. I think that's been something that has been talked about before.

Dr. VARMUS. Yes, we said a very similar thing last year, I agree with you.

Mr. ISTOOK. Yes, but you don't have anything more specific this year.

OMB CIRCULAR A-21

Dr. VARMUS. As I mentioned earlier, I think before you came in, we are waiting for a proposed revision of Circular A-21 from OMB. We expect to have that within the next few months.

Mr. ISTOOK. The next few months could mean two months or it could mean twelve months. I'm certainly not satisfied because I think, frankly, this is an issue that shortchanges areas that have lower cost-of-living unless there is a research differential or unless cost-of-living alone does not factor it out. I would think it would be extremely simple and should not take long at all to correlate against cost-of-living by itself so that then you know whether you need to be looking and how hard for other variables that might be at work.

Dr. VARMUS. I think we agree that there are multiple factors that determine the outcome. I should also point out to you that this is not solely an NIH matter, that this is a trans-government issue which I believe should be settled in a trans-agency manner.

COST OF ILLNESS

Mr. ISTOOK. Sure. The final issue I wanted to cover, Dr Varmus, and I know you published a report last fall that I think you revised a little later, "Disease-specific estimates of direct and indirect cost of illness and NIH support." It was referred to earlier that we don't want to be driven by death issues and say therefore whatever disease or category has the most deaths gets the most research funding. But as your report noted, it is a valid factor that needs to be considered.

I find that if you take the figures that were in your report and you simply graph them, these are the 15 top causes of death and 1991 was your survey period, it goes from heart disease to cancer, stroke, chronic obstructive pulmonary disease, injury, pneumonia, and so forth, HIV and AIDS, perinatal, and so forth. You see the pattern of course with that. But if you graph those causes of death and rates of death per 100,000 population and compare that with the actual funding, you would think there might at least in some places be some correlation. It's not just that there's none whatsoever that's so weak, but here you have heart disease causing this level of deaths and the amount of dollars, which in this case is \$2.77 per death of heart disease, compared to the one that sticks out which is HIV and AIDs, which is \$110.81 of research for every death. The point is not whether these correlate exactly, nobody would expect that, but you have here what is I think \$2 billion in research funds—

Dr. VARMUS. It is \$1.4 billion.

Mr. ISTOOK. Excuse me, \$1.4 billion, secondly only to the cancer funding. But this sticks out so much and it is so far down this list, it is between suicide and homicide on that. If you graph the same things against direct medical costs, \$1,000 worth of medical expenditures on these different diseases, the financial impact as op-

posed to the loss-of-life impact, again it is not as dramatic. Certainly cancer shows up better, liver disease prominent, HIV and AIDS though is runaway from there in that term of ratio.

In making the decisions of allocation of research dollars, and it's been discussed with all of us before and the authority that you desire, and these do not just reflect judgments of NIH, they are reflections of statutory directions from Congress and so forth. I well recognize that, but the question that I want to pose is, if you did not have congressional direction on things, do you believe that we would see any significant change in the patterns that are already here on which diseases are getting much higher ratios of research funding if the NIH had the authority to make those determinations?

Dr. VARMUS. That's a very difficult question to answer, Mr. Istook. But I don't believe that there would be a major change in the pattern. There would probably be some subtle changes but not major changes. I know that your attention is drawn to the amount of money that is spent on HIV/AIDS.

Mr. ISTOOK. Not because it's not a terrible disease but that it is one of many terrible diseases, of course.

Dr. VARMUS. Yes, but I think it's important to point out a number of features of HIV/AIDS that you and I have discussed before that are extremely important in the allocation of large amounts of resources in that area. First, it is an infectious disease, it is a new disease, it is continuing to spread in certain components of the population that had low rates before and now we're seeing higher rates, it's a major problem throughout the world.

Mr. ISTOOK. We got in that at hearings last year that actually showed that the bump in the reported cases was due to a change in the definition and then after that—

INCIDENCE OF AIDS

Dr. VARMUS. I understand that, Mr. Istook. That is not what I was saying. I did not say the rate overall had increased. What I was saying is that when you subdivide the population, when you look, for example, at heterosexual transmission or transmission in minority populations and among drug users, the rates have gone up even though the rates have fallen somewhat among white male homosexuals.

Mr. ISTOOK. These were where they had fallen in the population as a whole. We discussed that and it is in the record from last year.

Dr. VARMUS. But it is important to consider the potential effects of an infectious agent that is making headway in significant sub-populations of our country, and we have a major responsibility when a disease is spreading like wildfire in Asia and Africa—in part, because we care about those nations and, in part, because that's going to have an impact on our own fortunes.

Mr. ISTOOK. So you're saying the NIH research should be driven by international concerns rather than national concerns?

Dr. VARMUS. Not "rather than" but "in addition to."

Mr. PORTER. Mr. Istook, we actually went over your time by almost five minutes. We're going to have to stick within our schedule. Mr. Obey, if you would like to start and then perhaps we'll go to another member and then come back to you after you vote.

Mr. OBEY. I will only be able to be here for about five minutes and then I've got some other meetings. Let me make, Dr. Varmus, just one point with respect to AIDS. It seems to me that in addition to the fact that it is an infectious disease, it would also seem to me that one reason for heavy spending in that area is simply that we have had cumulatively over the years a good many billions of dollars spent trying to learn about all other diseases. This is a major threat to the health of people around the world, it is relatively new and, therefore, we start with a knowledge base that is significantly lower. It would seem to me that there is ample rationale for trying to play catch-up on a new threat to everybody.

ETHICS ASSOCIATED WITH GENETICS RESEARCH

I just want to go back to a concern that I voice frequently with you, and whenever you raise this question people have a tendency to respond by suggesting that you're a Luddite or something like that, and that relates to the genome project. We're making a lot of progress in completing that project. Ten years from now, what do you think we will understand that we didn't understand before we began the project? How will that be of help to individuals who have or are susceptible to various diseases that we're all concerned about? And how can that knowledge hurt individuals if the state of the law does not catch up with the state of the science on all of these questions relating to genetic research? And would you lay out for me your concerns about the state of the law in terms of the way that information can be used on top of the table or under the table by insurers, employers, other people with economic power in the society who like to use information for the benefit of their own financial bottom line?

Dr. VARMUS. Mr. Obey, I would never accuse you of being a "Luddite." Those are very important questions that you raised. I'm sorry you're only going to be here for five minutes because we can't really grapple with these complicated issues in a short period of time. Perhaps you will be on hand when Dr. Collins testifies next week.

With reference to the kinds of things we will know over the next ten years, perhaps the best guide is to look at what we've learned just in the last couple of years. These are guideposts to what we're going to be learning as the entire genome project reaches completion. First, we're going to learn about ways to alert people that they're at risk of certain diseases, and this is going to have a major impact on prevention. Secondly, we're going to learn about the mechanism by which disease arises. I alluded in my opening remarks to a recent discovery of a gene that is involved in the aging process. By looking at the way in which such genes operate, there are going to be very fundamental insights into pathogenesis, the pathways by which disease arises. I believe that's going to have major impact on the development of various kinds of therapeutics. For example, gene therapy is completely based on our ability to identify the genes that are responsible for diseases and try to develop new kinds of therapies.

Time does not permit going into these in great detail. I will respond very briefly though to your concerns about protecting individuals from abuse in genetic information. You and I, and Dr. Col-

lins as well, share a concern about these issues. Recently, the Equal Employment Opportunity Commission ruled that under the Americans with Disabilities Act genetic information can be considered a factor in determining disability. We are, of course, concerned about protecting individuals from insurance companies that would restrict their access to insurance and we are hoping that passage of some of the legislation that's currently proposed in the House and Senate will afford protection against abuse of genetic information by insurers and health service providers. But I agree with you that we do have work to do in these areas. Very few States have passed legislation that protects individuals from discrimination by employers and by insurance companies. As the science matures and hopefully even more quickly than that, we hope to have legislation in place nationally that will provide the kinds of protections that individuals deserve.

Mr. OBEY. We're out of time, but I would just like you to provide for the record a statement indicating what the range of legal and ethical issues will be as you see them and what kinds of changes we ought to have in place for the next decade to deal with these issues. Not that you need to do it yourself, but I would certainly like to have a comprehensive statement about what the challenges are if we're going to protect people from information that's supposed to help them.

[The information follows:]

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS OF HUMAN GENOME RESEARCH

For the next few years, the key ethical, legal and social implications (ELSI) arising from the Human Genome Project and human genetics research are privacy and fairness in the use and interpretation of genetic information, responsible clinical integration of new genetic technologies, study and resolution of issues surrounding genetics research, and public and professional education about genetics and genetic technologies.

The ELSI program includes several components that all work together to provide solutions to the key ethical, legal, and social issues. These components are:

1. The Extramural ELSI Branch, which supports research studies to examine ELSI issues and which has generated a rich body of scholarship and a cadre of well-informed experts in law, ethics, social science, philosophy, theology and public policy that will inform the process of policy development and implementation;
2. The NIH-DOE Joint Working Group on the Ethical, Legal, and Social Implications (ELSI Working Group) which provides overall guidance to the ELSI Program, facilitates policy discussions, and develops policy options and recommendations;
3. The Office of Policy Coordination which provides information and analysis of ELSI policy issues, sponsors policy workshops and supports the work of the ELSI Working Group.

The Ethical, Legal, and Social Implications program of the National Center for Human Genome Research is committed to the study and analysis of these issues, as well as any others that arise in the future, and the development of policy options and recommendations for changes needed to maximize the benefits and minimize the risks of genetic research.

Following are examples of the policy recommendations/activities in each of the priority areas.

PRIVACY AND FAIRNESS IN THE USE OF GENETIC INFORMATION

Health insurance

The ELSI Working Group has long been concerned about the fair use of genetic information, particularly as it relates to health insurance. In 1991, the ELSI Working Group created a task force on genetic information and health insurance, which recommended that insurers be prohibited from using genetic information to deny or limit health care coverage or services and ensure universal access to and participation in a program of basic health services (Genetic Information and Health Insurance, Report of the Task Force on Genetic Information and Insurance, 1993). More recently, the ELSI Working Group and the national Action Plan on Breast Cancer (NAPBC), a public-private partnership to address the research, education and policy issues in breast cancer, jointly addressed the issue of genetic discrimination in health insurance and developed a set of four recommendations for state and federal policy makers:

- 1) Insurance providers should be prohibited from using genetic information, or an individual's request for genetic services, to deny or limit any coverage or establish eligibility, continuation, enrollment, or contribution requirements.
- 2) Insurance providers should be prohibited from establishing differential rates or premium payments based on genetic information or an individual's request for genetic services.
- 3) Insurance providers should be prohibited from requesting or requiring collection or disclosure of genetic information.
- 4) Insurance providers and other holders of genetic information should be prohibited from releasing genetic information without prior written authorization of the individual. Written authorization should be required for each disclosure and include to whom the disclosure would be made.

Since publication of these recommendations in *Science* magazine in October 1995, several bills have been introduced in State legislatures and the U.S. Congress to address the issue of genetic discrimination in health insurance. Genetic information has been included in both the House and Senate health insurance reform bills among the factors insurers may not use to deny or limit health insurance coverage.

b. Employment

Since the inception of the Human Genome Project, members of the ELSI working group and the ELSI program staff have interacted with the US Equal Employment Opportunity Commission (EEOC) to express concerns about the lack of employment protections for individuals who might have a genetic predisposition to disease. In March 1995, the EEOC issued guidance that clarifies that protection under the Americans with Disabilities Act extends to individuals who may be discriminated against in employment decisions based on genetic information. The NAPBC and the NCHGR are initiating an analysis of the extent of protection provided by the EEOC guidance and will make policy recommendations where needed for additional protections.

c. Other Non-medical uses of genetic information

Genetic information could now, or in the future, be used inappropriately by social institutions such as schools, adoption agencies, and the courts. The ELSI program continues to fund research on how genetic information may be responsibly used in these settings, and the ELSI working group has initiated a study of non-medical uses of genetic information.

d. Privacy

As more genetic factors are identified as causes for and predictors of human disease, genetic information will increasingly be apart of people's medical record. There are currently no federal laws protecting the privacy of medical records though bills have been introduced in both the House and the Senate to protect the confidentiality of medical information.

CLINICAL INTEGRATION OF NEW GENETIC TECHNOLOGIES

As new genetic technologies are moving rapidly from research into clinical practice, concerns have been raised that not enough is known about the impact of genetic information on people's lives and health. The ELSI program has funded a number of research projects to examine the impact of integrating genetic technologies into health care practice and to develop recommendations about how best to improve knowledge and incorporate these technologies into general medical practice.

The ELSI program has sponsored two special initiatives in this area. The first, in 1991, supported studies on issues surrounding genetic testing and counseling for cystic fibrosis mutations. The second initiative was designed to stimulate study of issues surrounding genetic testing and counseling for heritable breast, ovarian, and colon cancer risks.

The Task Force on Genetic Testing of the ELSI Working Group is currently examining the state of genetic testing in the U.S. and making recommendations to ensure the development and delivery of safe and effective genetic tests. The Task Force, which has representation from consumers, professional societies, and experts in law and ethics, the biotechnology industry, and federal agencies involved with oversight of laboratory testing is examining the scientific validation of new genetic tests; laboratory quality assurance; and education, counseling, and delivery of genetic tests. The Task Force has already issued a series of interim principles for which public comment is being sought. The Task Force will next consider mechanisms for implementation of the interim principles. The Task Force is expected to complete its work and issue recommendations by late 1996.

ISSUES SURROUNDING GENETIC RESEARCH

Genetics research may result in the discovery of information that is powerful and potentially predictive. In addition, such information may have implications for other family members. While in some cases such information may be beneficial to research subjects and their families, there is also potential for misinterpretation or misuse. Special concerns have arisen about the process of informed consent for participation in genetics research, particularly when the risks and benefits of research may not be fully known. In response to these concerns, the ELSI program collaborated with the Office for the Protection of Research Risks to convene a workshop to develop guidance for investigators and Institutional Review Boards who were being asked to approve genetics research protocols. The deliberations of this workshop were published as a chapter on Human Genetics Research in the OPRR IRB Guidebook.

There has also been increasing concern about the adequacy of informed consent and privacy protections when stored tissue samples are used in genetic research. In response to these concerns the CDC and the ELSI program supported a meeting to explore these issues. The recommendations from this workshop were published in December 1995, in the *Journal of the American Medical Association*.

PUBLIC AND PROFESSIONAL EDUCATION

Most members of the general population and most health professionals are not knowledgeable about genetics, genetic technologies and the possible ethical, legal, and social implications of having genetic information. It is imperative that members of the public have an adequate understanding of the meaning of newly discovered genetic information. It is also essential that our nation's health professionals have the knowledge, skills, and resources to effectively integrate this new knowledge and these new technologies into the diagnosis, prevention, and treatment of disease.

The ELSI program has funded a number of educational projects for public education, K-12 education, education of policy makers and professional education. At the moment, the highest priority is health professional education.

A number of efforts have been made to educate health professionals in genetics and many of these efforts have been effective. Still, most genetics education activities for health professionals to date have been small in scale. These small-scale efforts now need to be supplemented by a coordinated, national effort to systematically educate all health professionals in genetics and the related ethical, legal, and social issues. Consumer and voluntary organizations, health professional organizations, and genetics organizations, as well as government agencies, will all be involved in a Coalition, catalyzed by NCHGR, to educate health professionals in genetics.

A more detailed summary of the first five years of the ELSI program is available upon request from NCHGR.

Mr. PORTER. We have to go vote and we'll be back as soon as possible.

[Recess.]

Mr. BONILLA [assumes chair]. The hearing will reconvene.

Mr. Dickey.

ISSUES OF DIVERSITY

Mr. DICKEY. Doctor Varmus, how are you? I want to get at this subject about what we're going to call whom and have it relate to something that is going to be a substantive issue later on, so be patient with me. I noticed as that list was being read that nothing was in there to ask anybody to be tolerant of people who call themselves Christians or who believe in the Bible or who say they're born again. Are you aware that there are some prejudices and there are some intolerant attitudes toward people who call themselves Christians?

Dr. VARMUS. I'm sure there are intolerant attitudes of all kinds.

Mr. DICKEY. Why would there not be then some reference to those people on that side in your agency?

Dr. VARMUS. Mr. Dickey, let me just state again that that was an article written by someone who is not even a member of the Office of Employment Opportunity. It is a personal statement. This does not reflect NIH policy. We're concerned about any discriminatory or prejudicial behavior and I would be intolerant of anyone who was to be critical of someone because of their religious beliefs.

Mr. DICKEY. In your discussions and in your studies and research and in your hiring practices and so forth, is there ever mention of God, His purposes, His part in creation, or His part in your projects?

Dr. VARMUS. As part of our hiring practices?

Mr. DICKEY. In any part. Do you ever mention God in your discussions?

Dr. VARMUS. Religion is not a basis on which we do hirings. We hire irrespective of people's personal beliefs.

Mr. DICKEY. If someone came in and said I'm a born again Christian and I want to make sure that this money is being spent not adversely to what I believe in, would that person be hired?

Dr. VARMUS. I can't imagine a situation in which that line of discourse would arise.

Mr. DICKEY. So it just never happens. You don't have those types of discussions, is that what you're saying?

Dr. VARMUS. I haven't in my own hiring practices. I can't vouch for those of other institute directors.

Mr. DICKEY. I'm sort of astounded by it. I think it makes a difference because of something we've talked about. Is there any chance that you could send a notice around saying there is nothing wrong with saying that you want to call your husband a husband or your wife a wife if that's a personal religious belief? Is there anything wrong with your sending that out and putting it on the bulletin board?

Dr. VARMUS. What was in that Journal article does not represent a directive from my office. It was simply a contribution to one of several magazines that have been published on our campus. That magazine happens to no longer be published.

Mr. DICKEY. Who paid for that?

Dr. VARMUS. The NIH.

Mr. DICKEY. Out of this budget?

Dr. VARMUS. Yes. The Journal in total costs less than \$15,000 a year. That Journal in its current form no longer exists.

Mr. DICKEY. I'm concerned that this much energy would be spent and this much attention be given to something that many individuals would find offensive to Christian beliefs.

Dr. VARMUS. Mr. Dickey, I don't think that the article is intended to criticize those who are in traditional marriages. The intention of the article, if you've read the whole thing, was to suggest that there were people who were in other kinds of domestic arrangements and that in some circumstances it might be appropriate to acknowledge those other kinds of arrangements. But I don't see any discriminatory language with respect to a traditional heterosexual marriage.

Mr. DICKEY. So you don't think there's any reason to send a notice back around and saying that even though that was the last edition, we do want you to know that if you want to call your husband a husband or your wife a wife, or if you want to say that you're born again or that you're a Christian, you can do that and ask other people not to be intolerant or not to roll their eyes or show impatience in that environment over there?

Dr. VARMUS. That article was the expression of one person's opinion. It was not an official NIH policy.

EMBRYO RESEARCH

Mr. DICKEY. All right. Let's talk about something we've talked about before then in that context—human embryo research. Do you know there are some people who are against spending money for that project on a religious basis? Do you understand that?

Dr. VARMUS. Yes.

Mr. DICKEY. Has that ever been discussed in your department?

Dr. VARMUS. Yes.

Mr. DICKEY. And is it still your attitude to go forward with it if you get funded?

Dr. VARMUS. At the moment we are respecting the wish of the Congress which has prohibited us from doing any human embryo research. As you know, Mr. Dickey, we had a large panel look at the benefits and problems associated with human embryo research for several months and they produced a report that was thoughtful and useful and made a number of recommendations about what was and was not appropriate for NIH to pursue. It weighed the potential health benefits of research in this area, it considered the fact that there were individuals who were opposed to such research on ethical and religious grounds, and made a series of recommendations that are viewed by some as too restrictive and viewed by others as too liberal.

LINK BETWEEN ABORTIONS AND BREAST CANCER

Mr. DICKEY. Let me speak of another issue. On March 20, we talked about a link between abortions and breast cancer. Do you remember that discussion?

Dr. VARMUS. Yes.

Mr. DICKEY. You said that you thought the connection was rather weak.

Dr. VARMUS. I did.

Mr. DICKEY. It is my understanding, however, that Dr. Janet Daling of the Cancer Research Center has published results of a 7 year study which shows that for women 18 years or older who had undergone an abortion after the eighth week of pregnancy, the risk of getting breast cancer before age 45 increased 800 percent. This does not appear to be a weak link to me. Can you explain how you think that's weak or how you can discount that 7 year study.

Dr. VARMUS. First of all, I don't believe that the increase was nearly as high as that. That was one study which did have some procedural weaknesses. In fact, the author herself was hesitant to draw conclusions that are very strong from the evidence at hand. Since then there have been additional reports on this topic which failed to find any link between abortion and breast cancer.

Mr. DICKEY. Do you have those studies?

Dr. VARMUS. I can submit them for the record.

Mr. DICKEY. I would like to have a copy.

Dr. VARMUS. We'd be pleased to do that, sir.

[The information follows:]

ABORTION AND BREAST CANCER

Three reviews published in the scientific journals *Epidemiologic Reviews*, *International Journal of Cancer*, and the *Journal of Epidemiology and Community Health* have concluded that the available data on the relationship between induced abortions or spontaneous abortions (miscarriages) and breast cancer are inconsistent and inconclusive. While some studies have indicated small elevations in risk, others show no risk associated with either induced or spontaneous abortions. Indeed, the biological rationale for an association between abortion and breast cancer is based on limited data from experiments in rats, and is not consistent with human data.

Those studies that have attempted to evaluate the association between abortion and breast cancer have been hampered by the small number of women in the study, the use of inappropriate comparison groups, the inability to separate induced from spontaneous abortions, and an incomplete knowledge of other potentially pertinent lifestyle factors. In addition to these difficulties, the most serious weakness with studies of this kind is the inaccuracy associated with reporting abortions retrospectively. Results from a study that examined the accuracy of self-reporting abortions indicate that women with breast cancer are more likely to accurately report having had an abortion than women who do not have breast cancer. Such a difference in reporting could potentially lead to a false association linking abortion to increased breast cancer risk.

An article published on November 2, 1994 by Dr. Janet Daling and others in the *Journal of the National Cancer Institute* studied the relationship between breast cancer and abortion for younger women. The results, based on self-reporting of abortions, indicated that induced abortion was associated with one-and-a-half times the average risk of developing breast cancer. It is important to note, however, that in epidemiologic terms, such an increased risk is considered to be relatively small as compared with the 1,000 to 2,000 percent increase for lung cancer risk that is associated with cigarette smoking. In addition, some inconsistencies in the findings of the Daling study proved to be puzzling: the risk did not vary consistently with the number of abortions, the mother's age at abortion, or the length of pregnancy, nor was there an increased risk shown to be associated with spontaneous abortions. An accompanying commentary by Rosenberg, in the same journal, concluded that "While the findings of Daling et al. add to the limited evidence that induced abortion increases the risk of breast cancer, neither a coherent body of knowledge nor a convincing biologic mechanism has been established." At the time of publication, the National Cancer Institute released a press statement about the article which concluded that "Taken together, the inconsistencies and scarcity of existing research do not permit scientific conclusions."

In the January 24, 1996 issue of the *Journal of the American Medical Association*, a report by Dr. Polly Newcomb and others showed induced abortions to be associ-

ated with a slight elevation in the risk (23 percent) of developing breast cancer. Noting the lack of strong evidence to support a cause-and-effect relationship, the authors themselves state that "... our data suggest that the risk of breast cancer associated with any pregnancy termination is likely to be small, if it exists at all." This article was also accompanied by a commentary that discussed the problems with interpreting data relating to the effects of induced abortion. It concluded by noting that "Although many investigators appreciate the complexity of the abortion-breast cancer issue and the methodological obstacles that prohibit a consensus at this time, the consequences of misinterpreting this limited information are already clear."

OTHER STUDIES ON ABORTION AND BREAST CANCER

In contrast to the articles by Drs. Daling and Newcomb, there have been a number of other recent epidemiologic studies which have failed to observe any relationship between induced abortion and breast cancer risk. In the latest reported study, published in the February 8, 1996 issue of the *International Journal of Cancer*, Dr. Alessandra Tavani and others reported a case-control study conducted between June 1991 and February 1994 in six areas of Italy which analyzed the relationship between spontaneous and induced abortions and breast cancer risk. The authors concluded that their results indicated no association between induced and spontaneous abortions and breast cancer risk in these women.

In summary, while there are a number of known factors that contribute to increased risk for breast cancer, no direct relationship between either induced or spontaneous abortion and breast cancer risk has been established. The risk of breast cancer increases with age, from about 1 in 2,525 for a woman in her thirties to about 1 in 11 for a woman in her seventies. Risk factors include a family history of breast cancer, early age at menarche, late age at menopause, late age at the time of the first full-term birth of a child, obesity, and certain breast conditions. The increase in risk of developing breast cancer associated with each factor varies, from 50 to 300 percent. For this reason, it is important for women to discuss their individual risk of breast cancer with their personal physicians.

Mr. DICKEY. Those are all the questions I have. Thank you, Mr. Chairman.

Mr. PORTER [resumes chair]. Thank you, Mr. Dickey. Mr. Riggs.

FY 1996 BUDGET INCREASE

Mr. RIGGS. Thank you, Mr. Chairman. Good afternoon, Doctor Varmus. I am going to be brief in my questions because I think, as do a lot of us now, we're concerned about travel connections. First of all, I would like to get clear in my mind, as you've acknowledged in your testimony, you received a 5.8 percent increase for fiscal year 1996 over fiscal year 1995. Is that a 5.8 percent increase for both NIH and CDC?

Dr. VARMUS. No. That's just NIH.

Mr. RIGGS. Just NIH. I would like to go back to last year's budget request. How much did you and the President request for fiscal year 1996 in terms of increased funding for NIH?

Dr. VARMUS. Roughly, 4.2 percent.

Mr. RIGGS. So you actually received a 1.6 percent increase over and above the 4.2 that you were requesting?

Dr. VARMUS. That's correct.

Mr. RIGGS. Roughly, what does that amount to in actual dollars?

Dr. VARMUS. It is approximately \$200 million. I'm told it is \$165 million. [CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this figure to \$175 million.]

Mr. RIGGS. How are you spending that additional money?

Dr. VARMUS. Actually, the chart on the easel shows some of this. Most of it has been devoted to research project grants. There have been increases in many of our research mechanism categories. We

have tried to use some of that money to move ahead on initiatives in certain areas—neuroscience, aspects of cancer genetics, and a few other areas that we had identified during deliberations over the 1997 budget request.

Mr. RIGGS. Did any of that additional 1.6 percent go to AIDS-related research?

Dr. VARMUS. Very little.

FUNDING HISTORY: PROJECTING THE FUTURE

Mr. RIGGS. It would be helpful to me as a relative newcomer to the subcommittee to get more of a long-term look at NIH funding; that is to say looking back over the last several years, but, more importantly, projecting out into the future where you see the true need for continued taxpayer support of biomedical research, and then breaking down—I think the Chairman has developed the correct policy, I think it is quite appropriate that we fund you on a lump sum basis and then you decide how you're going to break that down across the various or different institutes. But I would really like to get an idea of where we're going here. One of my frustrations as an elected policymaker is that long-term planning in Washington, DC is election cycle to election cycle and we rarely look out much beyond the next election. This is too serious and too important an area I think to be talking in two year increments of time. So, again, I would like to take the longitudinal look, if that's the right term, and would like to have that information as we go into our deliberations for your fiscal year 1997 budget.

Dr. VARMUS. Of course, it is very simple for us to provide you with those numbers. Just as a matter of index, NIH grew at quite a rapid rate in the 1950s and 1960s and somewhat less rapidly in the 1970s. In the 1980s, growth slowed further, and over the last several years we've been just very slightly ahead of inflation. We have tried to adapt to this new steady state environment. We recognize that there are tremendous opportunities in biomedical research. But with the reduction in revenues for research at academic health centers consequent to the influx of managed care plans, we are feeling the stresses even more than before. We are trying to adapt to the demands placed upon the Congress, which is attempting, of course, along with the administration, to achieve a balanced budget. We recognize all these forces are constraining us and so we're trying to do the best we can with the money that is being made available. We think it is of absolute importance that we try to maintain pace with inflation. We would be happy to discuss with you ways in which we can try to forecast where we'll be five or ten years from now.

FUNDING PRIORITIES

Mr. RIGGS. Again, I think that would be very important. I will say for the benefit of the Chairman and Mrs. Lowey, that I just hope that we can avoid, being placed in this position of having to make a Hobson's choice between programs that some of us feel are very important and worthwhile, and I'll just mention a quick example. I'm an advocate of universal early childhood education, so I don't like the notion that I might have to cut Head Start funding to increase or plus up NIH funding. I hope we can avoid a repeat

of last year or this year or wherever we are and get some bipartisan agreement to increase the funding, if you follow what I'm saying.

I thought we had perhaps a window of opportunity, and, of course, the Chairman and the members of the subcommittee have to work with the 602-B budget allocation figure we're given, as you do—and my hands are clean on this. I voted against the Defense appropriations bill and the B-2, not easy to do necessarily as a Republican member of the appropriations committee—but I thought that we had perhaps an opportunity there with the \$8 billion more in defense spending than the Pentagon and Joint Chiefs said were necessary until the President of course reconsidered his position when he decided, and this is certainly his call, that we needed all or a big part of that \$8 billion to pay for our Bosnian mission. So I hope all of us can work together going into this year's budget deliberations to avoid a repeat of last year where, again, we're not having to take the money from Head Start to pay for an increase for NIH.

Mr. PORTER. Thank you, Mr. Riggs. Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman. Are we doing eight or fifteen minute rounds?

Mr. PORTER. We're doing eight but you and I are the only two left here, so. [Laughter.]

RESEARCH BENEFITS

Mrs. LOWEY. Thank you, Mr. Chairman. I want to thank you, Doctor Varmus, for your testimony. It is certainly a pleasure for me to see you this year. As you know, I've been a very strong supporter of the National Institutes of Health and I want to thank the Chairman for his extremely strong leadership in this issue. I know if it were up to the two of us here, maybe we can do it while no one is here, Chairman Porter, we would probably double the increase for the National Institutes of Health. So I just want to thank you for all your extremely hard work. I also want to say as a representative of New York where we have such extremely outstanding medical research institutions such as Cornell and New York University, maybe I better not keep going because I'm going to leave some out, I am very much aware of the benefits of the support of the research provided by the National Institutes of Health. It is critical not only to our country as a world leader in research, but it's an important factor in the economy of the New York region. So I want to thank you.

As co-chair of the Congressional Caucus on Women's Issues and a long time advocate for women's health issues, I just want to tell you we've come a long way. I do believe that the National Institutes of Health is making progress in decreasing the inequities faced by women's health. For example, I'm aware that the NIH is moving forward on the issue of inclusion of women and minorities in clinical trials. The Office of Research on Women's Health, which is part of your office, Dr. Varmus, is to be commended for its hard work on this issue. We certainly have challenges ahead, I don't want you to think everything is terrific, but I look forward to continuing to work with you on women's health issues. We just want

to be sure that they continue to be treated seriously, and we know they are.

BREAST CANCER FUNDING

I want to ask you a question first on breast cancer funding. As you know, I have been deeply involved in advocating for increases in breast cancer research and in making sure our investment is well spent. Can you tell us how much the National Institutes of Health is planning to spend on breast cancer research in fiscal year 1997, and how does this compare to your investment in fiscal year 1996?

Dr. VARMUS. The numbers that have been determined by the Institutes for 1997 would total about \$409 million. I would point out to you that those numbers have grown from a number of \$228 million in 1993. We've gone through a very rapid increase in our support for breast cancer as a result of presidential initiatives over the first few years of the Clinton term. We feel at this point we have reached a level of funding for breast cancer research that is adequate to handle the excellent applications that we receive. There are, of course, many major discoveries that have occurred in the area of breast cancer research over the last few years—among them the isolation of the BRCA-1 and BRCA-2 genes that I'm sure you're familiar with—but also many other discoveries about the pathogenesis of cancer, detection of cancer, and its treatment as well. So we're very optimistic. You'll hear from Dr. Klausner about recent evidence that breast cancer death rates are beginning to decline in all segments of the population. We're very encouraged by that. There are new means for trying to detect early breast cancer and to distinguish benign from malignant lesions using ultrasound. There is tremendous interest in trying to make good use of the new genetic information that's become available. So we feel that the program is extremely successful at the moment, and we feel we're funding excellent proposals with this significant increase that's occurred during the first years of the Clinton Administration. We thank you for your support.

Mrs. LOWEY. And I thank you. I'll save my questions concerning the ethical challenges and the health insurance challenges that are connected to all these exciting new discoveries for either Dr. Klausner or when we get to talking about the gene research. But I'm very well aware of the genetic information issue and I would like to work with you on that.

DIABETES RESEARCH

For those of us who are involved in advocating for diabetes research, we want to ensure that the NIH will continue to make a sufficient investment in eradicating this disease. How would you respond to the criticism which I have heard that diabetes and diabetes-related research at NIH has fallen fairly steadily as a percentage of the total NIH research since the late 1980s even if we take into account the budgets which were added to NIH as a result of the creation of several new institutes? I always hesitate to ask you these questions because I'm aware that we're constantly comparing one investment to another, but you know the advocates are

out there comparing one line to another. How would you respond to that challenge?

Dr. VARMUS. Well, in two ways. First of all, as I look at the numbers, there is an increased number of dollars in that area. Whether some areas have received slightly more than others I think is hard to judge. I also think it is difficult to make judgments based on these numbers because they often fail to take into account the contributions that one field makes to another. For example in the area of diabetes, it is extremely important that we understand the relationship of diabetes to genetics research, or diabetes to cardiovascular disease, or the relationship of diabetes to infection, because many other fields have an effect upon our progress in a disease like diabetes which affects so many organs. Another example of course would be the role of the study of eye disease upon diabetes. As you know, one of the major consequences of long-term diabetes is disease of the eye or disease of the kidney. There are efforts in the study of those organs that are sometimes accounted for as diabetes but sometimes assigned to other categories of research.

We've had a very useful relationship with the Juvenile Diabetes Foundation and with other diabetes advocacy groups in attempting to use our money more effectively in conjunction with those organizations. For example, a number of institutes have signed agreements with the Juvenile Diabetes Foundation that allow the establishment of diabetes centers co-funded by the NIH and by this private agency. These joint efforts are allowing us to carry our efforts further in conjunction with organizations that have a direct interest in diabetes.

Mrs. LOWEY. It would be very helpful if I could have an expanded response to that, so I can be more helpful to you.

[The information follows:]

DIABETES RESEARCH

In FY 1991, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Foundation International (JDFI) joined forces to support a new Diabetes Interdisciplinary Research Program for insulin-dependent diabetes mellitus (IDDM). The NIDDK issued a Request for Applications for program project grants that would incorporate an interdisciplinary research approach to the cause and course of IDDM, or to the genetic susceptibility for the long-term complications of IDDM.

The solicitation was intended to stimulate the application of advances in basic molecular biology, genetics, immunology, cell biology, and biophysics to the study of IDDM and its complications. A special NIH initial review group was established to evaluate the applications, and six grants were awarded in FY 1992. The NIDDK funded two of these program project grants, and the JDFI supported the other four additional projects.

In FY 1994, the second RFA for this program was issued by the NIDDK and the National Institute for Allergy and Infectious Diseases (NIAID), with the same research goals and objectives as the first solicitation. In FY 1995, eight new grants were awarded. The NIDDK funded three program project grants, and the JDFI funded five projects. The NIAID contributed funding to two of the NIDDK projects. Scientific workshops for this program are held annually as a way for DIRP investigators to share and discuss their current research with each other and with NIDDK and JDFI staff.

The NIDDK anticipates that the DIRPs will accelerate the introduction of the most modern scientific techniques into diabetes research and will facilitate their clinical application. This collaborative effort has increased the funds available to the diabetes research community. The program project grants are pursuing innovative research, for which the program project framework is most conducive.

CLINICAL RESEARCH

Mrs. LOWEY. Last year, the committee reports accompanying both the House and Senate Departments of Labor, HHS, Education bills asked that you move forward to implement the recommendation of the Institutes of Medicine on clinical research. This subcommittee asked you for a report by January 1 of the progress made on three IOM-recommended initiatives—the expansion of clinical research training opportunities, the expansion of the NIH general clinical research centers program, and the development of a loan repayment program to assist young physician-scientists with their medical school tuition debts. Has that report been submitted? If not, when is it expected? Can you give us some idea of what you will report? Also, as you know, legislation has been introduced in the Senate by Senator Hatfield to implement some of the IOM Committee's recommendations. I would be interested to know the position of the NIH on this bill.

Dr. VARMUS. Let me just make a few points about your comments. I was just out in Portland, Oregon, last week to attend a hearing that Senator Hatfield had arranged in his home State about clinical research. I made a number of points on that occasion that are relevant to the question you've raised. We do have a loan repayment program, as I mentioned earlier, that is serving trainees in clinical research at the NIH. We would like to have authorities to institute loan repayment programs for extramural clinical trainees as well; we don't have those authorities as yet. We do support mechanisms, a so-called KO-8 award in particular, that support people who are clinically trained and who are entering research careers. I have just been supplied with our response to the IOM report which has been sent to the Department, and apparently the Department sent it to the committee two days ago. So you probably have not yet seen it, but it is on the way.

Mrs. LOWEY. Thank you.

Dr. VARMUS. I would draw your attention to a clinical research panel of about a dozen or more distinguished clinical investigators, chaired by Dr. David Nathan from the Dana Farber Cancer Center, who have been helping me to carry forward many of the initiatives that we believe are necessary to improve the status of clinical investigation in this country. Many of the things that are raised by the IOM report are under consideration. We are reviewing the places where clinical research is done, such as the General Clinical Research Centers, we are looking at the training programs that exist in many places and seeking ways to improve them, and we're looking very closely at the mechanisms that exist to support clinical research. As I've repeatedly mentioned, we are of course concerned in particular about the loss of revenues at academic health centers that have resulted from the change in health care reimbursement. So in conjunction with our advisory panel, we are trying to respond as best we can within our resources to many of the recommendations that we believe are sensible.

MANAGED CARE

Mrs. LOWEY. I did want to pursue that particular question because I'm very concerned about the loss of revenue. What is the

NIH recommending and doing to address the problems that are being faced by our teaching hospitals in this fast-changing and increasingly profit-oriented world of health care? I meet with groups of physicians and researchers constantly and this is only one area of great concern in this changing health care world. So perhaps you could expand upon this issue.

Dr. VARMUS. Yes. Well, of course, there are two kinds of impact that result from the advance of managed care in health care provision. One, of course, is the monies themselves, and we cannot supply the difference between what was being received before and what is being received now. That may total as much as \$1 billion per year at the academic health centers throughout the country. We are trying to provide moral support for the idea that managed care plans take into consideration the long-range benefits of post-graduate medical education at those centers and the research activities that go on there. But, as you know, at the moment this is a do-or-die environment in which managed care companies and insurers are competing for health care markets. It is a very difficult time in which to ask them to consider the long-range impacts of what they do.

The other part of the issue has to do with access of clinical investigators to patient populations for conducting clinical research. Here, we have made——

Mrs. LOWEY. May I interrupt one minute, I'm sure the Chairman and I are most interested in this. Maybe it shouldn't just be back-door. Maybe either through a policy which we impose on the HMOs or a separate funding stream, I'm not sure that we should be dependent on the generosity and the sagacity of the HMOs to see the future of research. Perhaps this is an issue that we can pursue, whether it is a revenue source that would come from the HMOs or through the several pieces of legislation recommended here. But before you go on to the second alternative, I'm not sure that we should appeal to the generosity and the long-range vision of the HMOs for them to generously contribute to the academic teaching hospitals.

Dr. VARMUS. As you know, Mrs. Lowey, my powers are more limited than your own. [Laughter.]

Legislation could be enacted which would have an effect on the way in which money is generated.

Mrs. LOWEY. Well, this committee may just find—you said a \$1 billion loss—another \$1 billion to assist the academic teaching hospitals. But in any event, why don't you respond to the second part.

NCI/DOD REIMBURSEMENT AGREEMENT

Dr. VARMUS. In the context of patient recruitment, we believe that we can persuade some of the health care providers of the wisdom of paying for care that occurs during a clinical trial. You will hear from Dr. Klausner when he talks about the doings of the Cancer Institute of a landmark agreement that was recently reached between the Department of Defense and the NCI to allow the Tri-Care/CHAMPUS insurance mechanisms—which affect nearly 8.3 million people who are either in the Department of Defense or are family members of people in the Department—to allow those who participate in NCI-sponsored trials to be reimbursed for their medi-

cal care through the Tri-Care/CHAMPUS system. This is a three year pilot project, but we see ramifications of this model for other diseases or through other agencies, including Government agencies, private insurers, and managed care plans. Our hope is that we will be able to demonstrate that the additional cost burden is slim, if any, and that through this demonstration project we can encourage much broader use of traditional reimbursement plans in the context of clinical trials.

Mrs. LOWEY. Thank you. Thank you, Mr. Chairman.

SMALL BUSINESS AWARDS

Mr. PORTER. You're welcome, Mrs. Lowey. Dr. Varmus, let me talk about a few of the nuts and bolts. First, a number of outside groups, including Federation of American Societies for Experimental Biology, have come in to testify regarding SBIRs, the Small Business Innovation Research grants, saying that the grants funded are generally of lower quality than other research grants and many are not renewed for their second phase. I wonder if you can give us your feeling about this provision of the law and what you would suggest that Congress do with respect to it.

Dr. VARMUS. We recognize the virtues of the Small Business grants but we also have to point out that the priority scores for many of the grants that were funded in 1995 fall significantly below the priority scores for the traditional Research Project grants that come from research institutions and academic centers. The priority scores that are achieved by successful SBIR applications, of course, vary considerably among the different institutes, but I am frankly concerned that we may be funding a significant number of SBIR grants that are not up to the high quality of some grants that are not being funded in our more traditional constituencies.

We are now obliged to increase the number of these grants by 25 percent. This increase is going to cost us roughly \$40 million of our increase [CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this figure to \$43 million for the record.] in the RPG pool for 1997. We are following the administration's recommendation that we continue to abide by the original congressional directive to increase the level to 2.5 percent in this year and we are asking for that increase, but I do have a residual concern that you and I have discussed before.

Mr. PORTER. We have been reluctant to step on the toes of the authorizing committee regarding the set-aside and did not take that step last year. Because we understand some of these grants are not in the lower quality category, what if we were simply to limit the funding which is within our jurisdiction to say not more than a certain number of dollars were to be spent on SBIRs? And if we were to do that, what figure would you plug in to that formula?

Dr. VARMUS. I'm not sure I understand your proposal, Mr. Porter.

Mr. PORTER. We would simply put in the bill language that no more than x number of dollars can be spent for SBIRs and you would be limited to that amount and to its allocation. In other words, what I am really asking you is, how much of the money

spent for SBIRs now is money that would pass muster without the set aside that is good research and ought to be funded anyway?

Dr. VARMUS. Well, it is certainly more than half, roughly two-thirds. I think it might be possible to exchange grants among institutes and try to upgrade the quality. Of course, each year is different and it is hard for me to judge how far down the priority list it will be necessary to go to fulfill the authorizing committee's suggestion for 1997.

Mr. PORTER. It really involves, according to our figures, \$230 million in the 1997 budget.

Dr. VARMUS. That's correct. It would be about \$40 million over 1996 in a year when we are, frankly, constrained and looking for ways in which to conserve money to go to our highest priority grants.

Mr. PORTER. This is just in its initial thinking phase, but we would like to work with you on that and see if we can't make more sense out of this than simply a set aside that does not take into account the quality of the research being funded.

COMMONALITY OF RESEARCH

Dr. Varmus, we've read your testimony before the Senate NIH reauthorization hearings. You seemed to present NIH in a way that emphasized the commonality of research across institutes and you organized the testimony in themes like chronic disabling diseases and neuroscience research. What are you doing to break down the traditional boundaries between the institutes and encourage more collaborative work on campus? The second question, was your testimony a broader hint to Senator Kassebaum and her committee that they might consider reorganizing NIH around broad research areas rather than the way it is organized now?

Dr. VARMUS. The answer to the second question, Mr. Chairman, is no. With respect to the first question, one of the most useful changes that has occurred on the NIH campus in the last couple of years is the organization of what are called special interest groups. These are groups that were first envisioned by a report written by a panel chaired by two of the individuals now in this room, Bill Paul and Rick Klausner, when they were asked to write a review of the intramural program taking into account the views of intramural investigators. These special interest groups now number about 50. They have achieved much more interaction across Institute lines, interactions that are based on disciplinary similarities. I think it has reinvigorated the program, allowed better mentoring, better selection of seminar speakers, more effective working groups on campus, much more collaboration. I think it has created a healthier research environment on the campus.

ECONOMIC BENEFITS OF RESEARCH

Mr. PORTER. Last fall, you asked a group of outside experts headed by Dick Zeckhauser of Harvard to consider the question of measuring the economic benefits of NIH research. Their initial deliberations seemed to emphasize the difficulty of such measurements and even called into question some of the assumptions we take for granted such as that biomedical research decreases health care costs. What is your view of this group's initial discussions and what

are their next steps? Do you plan to fund some of the economic analyses that they have suggested?

Dr. VARMUS. We haven't yet decided whether to fund some of these initiatives, but we are considering through our Office of Science Policy some additional things that we might do. We are looking for ways to develop some models for how NIH research affects other fields, look at some examples in depth, look at the effects of patents that cite NIH research to see whether there are economic benefits that are not being measured by current studies. We did learn from that discussion that most people, including economists, finally justify NIH not on grounds of economic benefit, but on grounds of improved health, greater knowledge, and those are of course the goals with which most of us went into this business in the first place.

The economic impact is much more complicated. I think many of us felt a little frustrated at the end of that round table about being able to make a simple economic justification, despite the fact that one can also point to clear examples where the benefits can outweigh the expenses of funding the NIH. So there's no doubt that an evaluation of a single technology that makes health care more expensive, comes out of NIH-sponsored research, provides certain health benefits, and extends life may be very difficult to analyze. There are other examples where the benefit is so clear that there becomes less need to try to understand the intricacies of the more complex arguments.

SCIENTIFIC MISCONDUCT

Mr. PORTER. I realize that this is an issue that involves the entire Department, but what is your personal view of the recommendations on scientific misconduct made by the Ryan Commission? Would you support or oppose a return of the Office of Research Integrity to NIH from the Office of the Secretary?

Dr. VARMUS. We do not particularly want to see a return of the ORI to our organization, since I don't believe it should be embedded in the organization that does the research. I have some concerns about the Ryan Report. I believe that before it is acted upon by the Department that it ought to be subjected to a broader review by the many government agencies that are involved. To that end, the Committee on Fundamental Science which I co-chair with Neal Lane, the Director of the National Science Foundation, has taken on a responsibility to review the Ryan Report by a subcommittee chaired by France Cordova, the Chief Scientist at the National Aeronautics and Space Administration. We are looking at the contents of the report, a number of responses that have been received from the National Academy of Sciences, Federation of American Societies for Experimental Biology, and from other interested parties.

Mr. PORTER. Mrs. Lowey, do you want to ask some questions now?

BREAST CANCER FUNDING

Mrs. LOWEY. The hour is late and perhaps I will just pursue one comment you made with one question. I was concerned with your

response in terms of the 1997 dollars for breast cancer. I would be interested to know the 1996 dollars.

Dr. VARMUS. Sure.

Mrs. LOWEY. Secondly, granted there has been progress made, but the 1 in 8 is still 1 in 8. Perhaps the mortality rate has decreased slightly, you also mentioned great optimism, and I share it, about the discovery of the BRCA genes, but we both know that it affects about 5 percent of the population so there is still 95 percent of those women who get breast cancer who, with information to date, their disease is not connected to the BRCA genes. We don't know what tomorrow will bring with research. So although we've made progress and there's a feeling of optimism and women are detecting breast cancer earlier, I would hope that we don't get too sanguine and turn our attention to other things. We must keep the momentum going because those of us who have been in the front line of this fight would love to be here someday when we can end the scourge of breast cancer. We know that there are other battles to be fought in so many other areas, but I hope in this particular area where we've made so much progress we can continue to move ahead. I would just make that comment.

Dr. VARMUS. Mrs. Lowey, in making my comments about what I see as clear progress in the area of breast cancer, I didn't mean to be overly sanguine. In mentioning that the BRCA-1 and 2 genes have been isolated, I didn't mean to give the impression that we would no longer encounter disease that resulted from the inheritance of mutations that affect those genes. In fact, one of the current dilemmas is that we know very little about how to protect individuals who have mutations of those genes from the risk that they have incurred by the inheritance of the mutant forms of the genes. But it does give us something to work with, ways to do risk assessment, and ways to understand how the disease arises that I believe are extremely important.

To answer your specific question about the increase. In 1996, we had originally estimated spending at \$426 million. We now have adjusted that number down to \$403 million because we're finding, frankly, that within the institutes that are doing breast cancer research that we're unlikely to have enough outstanding applications to warrant that high an expenditure.

I want to draw your attention, however, to an important point that I have made frequently here and elsewhere: it is very difficult to categorize research as breast cancer research. We all know from our experience in research that what will benefit breast cancer is sometimes not initially labeled breast cancer research and vice versa. I myself have worked on a breast cancer in the mouse for many years. Perhaps our most important discovery in all that time was the discovery of a class of genes that appears to be extremely important in the development of the brain and the limbs. Although it is involved in breast cancer in mice we have no reason to believe at this point this class of genes plays a role in human breast cancer. Nevertheless, for those studying developmental biology or neurobiology, this class of genes is extraordinarily important. So we expect benefits to flow in both directions. Our own charge, as officials responsible for expenditure of biomedical monies, is to be sure

that the most promising science gets funded because we think that that's the way we will achieve the greatest benefit.

Mrs. LOWEY. I just want to make it clear that I ask these questions with the greatest respect for your expertise and for the scientists at the National Institutes of Health, for Dr. Klausner and the National Cancer Institute. But I am also aware as a member of this committee that there are areas that have been neglected for far too long. And although on the one hand I'm aware that the scientists feel that advocacy has too great a role in influencing decisions at the National Institutes of Health, on the other hand I remember the days in 1989 when clinical trials were not done on women because people felt it was too complicated, and when there were only three female gynecologists on the staff at the National Institutes of Health.

So, with the greatest respect for your leadership and that of the scientists, I would just hope that because of this extraordinary progress that has been made we can continue the momentum we both have alluded to, and I hope we continue to work on it together, including the tremendous challenges posed by the breast cancer gene. It is frightening to me, in talking to women in my district, the hysteria that you're hearing, the lack of adequate counseling of people who are having breasts removed prophylactically, and the publication just recently of the fact that commercial firms are going to be doing the testing. Because if someone has a predisposition and they find the gene, they don't know if they're going to get breast cancer. I don't believe that science has told us whether they're going to get it in ten years or fifty years; I don't believe we have this information as yet.

So, in conclusion, I guess I am applauding you for your tremendous leadership, for the work that's been done. I wish that Chairman Porter and I could double the funds for the National Institutes of Health, double the funds for mental health, for juvenile diabetes, for the National Institute of Mental Health, and on and on and on. But I just want to be sure that the tremendous progress continues to move ahead, and I look forward to working with you and all the other outstanding members of your organizations.

Dr. VARMUS. We believe we can do great things in this area. I hope you will be on hand when Dr. Klausner describes some of the plans for looking more closely at some of the unresolved questions with respect to BRCA-1 and 2 that you've alluded to. They are very appropriate.

WOMEN IN CLINICAL TRIALS

Mrs. LOWEY. I certainly look forward to that.

Dr. VARMUS. I must, however, make one comment about your statement about clinical trials. There were, in fact, a couple of very important clinical trials in the past that did not include women. It is not the case that there were no clinical trials that included women. The fact that there were any that excluded women is cause for inclusion guidelines; we feel that has been very successful, and I applaud your role in that. But I don't feel it is fair to characterize the situation in 1989 as one in which no women were included in clinical trials.

Mrs. LOWEY. You are correct and I stand corrected. I think I did compliment you and the Institute on the tremendous progress you've made in that regard and I thank you.

Mr. PORTER. Mrs. Lowey, I wish that Ms. Pelosi were here, and I wish a number of other people on our side of the aisle were here also. Because in all the 15 years prior to this year that I served on this subcommittee I always thought it was implicit that we understood there would be nothing more destructive than to set disease against disease with Congress by amendments adjusting between institutes, taking from one and giving to another and making our political decision as to where the funds ought to go. Now we're in a different budgetary environment and I am afraid that that implicit understanding may be under great siege. I don't believe that NIH doesn't make mistakes; you do make mistakes. But I believe that Congress would make a lot more mistakes than you would ever make. I think that we have to trust to the integrity and the good judgment of science in making these allocations. And, yes, we're going to send our messages and you're going to hear our messages, and we write them into the report very strongly and we feel strongly about them, but in the end I think we would be making a terrible, terrible error if we were to sit here and move all these funds around and say our judgement is better than your judgment, because it just isn't. I know I'm going to have a hard job convincing a number of people on our side that that's the case.

Mrs. LOWEY. I share your concerns and I look forward to being a strong ally with you, Mr. Chairman, in increased support for the National Institutes of Health. Frankly, for those on the other side who are concerned about cuts and wise investments, if we really want to cut health care costs and save our dollars, I don't think there's any greater investment than the National Institutes of Health. I just want to thank you again for your outstanding leadership.

SUCCESS RATES

Mr. PORTER. Thank you, Mrs. Lowey. Let me ask some final questions, Dr. Varmus. We often hear from the outside research community about the low success rates for researchers applying for NIH grants. Yet, a recent article in the Journal of NIH Research indicates that for some research mechanisms success rates are fairly high. The one problem area is RO-1s, the basic investigator initiated grant. Does this imply that the RO-1 funding pool has been diluted by the funding of other mechanisms such as program project grants?

Dr. VARMUS. I'm not sure diluted is the right word, but there is little doubt that the lowest success rates for certain institutes tend to be in funding RO-1's, especially RO-1's from new investigators. Rates in those categories can be as low as 10 or 12 percent. And it is also true that certain kinds of mechanisms, for example training grants, centers, and program project grants, have considerably higher rates. It is also true that when there is a formal Request For Applications, the success rate may be higher.

It is important to emphasize that it would not be appropriate for the NIH to say that we will move money out of those categories where the success rates are higher into RO-1's in a peremptory

fashion. Many of those programs are extremely important. To put together a center grant request for example, already requires that the applicants have a fairly high level of expertise in an area. Sometimes those grants are only accessible to those who have already achieved a level of success in other kinds of programs, for example, award of a center planning grant. So it is not straightforward to extrapolate from success rates to the level of merit. To be able to put together a training grant, for example, requires that there be a high level of expertise on campus, by several RO-1 supported investigators. So there is a pre-selection for applicants that already have shown success and are in a position to apply for these other grants.

Of course, it is important that we have training grants and centers and a number of other mechanisms, because we believe that there are special advantages to some of these grants. I have, in general, argued that we should look very critically at program project grants, centers, and we should look very critically at RFA's, and whenever possible, move money into the free market of unsolicited RO-1's where I believe we do get our best returns on our investment.

BRIDGE GRANTS

Mr. PORTER. How about moving money into Bridge Grants, what do you think of that?

Dr. VARMUS. The so-called Bridge Grant is a tool which can allow investigators who are doing important work and have been successful in carrying out research in the past on NIH grants to carry on when they've not met the necessity priority score for continued funding. My own view is that so-called Bridge Grants should not be given to the institution. Instead, on a case-by-case basis, the NIH institutes should be prepared to try to extend to some grantees who have failed in the renewal process money that would allow them to carry on. We know that investigators who come in just below the pay line are very likely to be successful in the next round of review. It is a good investment for institutes to provide such investigators with money to prevent the disaggregation of a successful research team. In most cases, that money is not extra money because it would be then deducted from the cost of the entire award once the award is made, and there's a very high likelihood that an award will be made.

Mr. PORTER. But you're not doing that now?

Dr. VARMUS. Yes, we are.

Mr. PORTER. You are doing that now?

Dr. VARMUS. Yes, we are. We don't know the exact number of such bridge awards, but they are being made by the institutes in many cases, probably several hundred a year, to keep investigators in business until their grant problems are settled.

Mr. PORTER. And how long have you been doing this?

Dr. VARMUS. For years.

Mr. PORTER. For years?

Dr. VARMUS. Yes. It varies among the institutes.

Mr. PORTER. Can you give me for the record a list and volume of that, not a list by project but by institute?

[The information follows:]

NATIONAL INSTITUTES OF HEALTH—BRIDGE GRANTS

(Dollars in thousands)

Institute	Number	Amount
NCI	92	\$5,002
NHLBI	17	1,136
NIDR	7	304
NIDDK	29	2,357
NINDS	3	171
NIAID	0	0
NIGMS	5	473
NICHD	21	1,407
NEI	9	526
NIEHS	4	948
NIA	13	1,017
NIAMS	0	0
NIDCD	0	0
NIMH	9	974
NIDA	4	255
NIAAA	6	268
NINR	0	0
NCRR	0	0
NCHGR	1	153
FIC	0	0
Total	220	14,991

Dr. VARMUS. I am aware that you have heard testimony and received correspondence about the possibility of creating an institutional award that would allow the institutions to make such decisions. I am concerned about that possibility, because I think that would involve a considerable amount of money and remove the award authority from the Institutes where I think it ought to reside.

FETAL TISSUE RESEARCH

Mr. PORTER. Some in the community fear that fetal tissue research which was authorized in the last NIH reauthorization may be revisited in the reauthorization process this year. For the record, can you tell us how much fetal tissue research NIH is funding and the reasons it is important not to squelch this type of research.

Dr. VARMUS. Well, let me first of all point out that there are really three kinds of fetal tissue research—research that's being carried out in the laboratory without clinical application, the pre-clinical activities which don't involve treatment, and then treatment activities for which there are only a small number of awards. The total amount spent on grants that involve some component of fetal tissue research is roughly \$25 million. That number is a slight over-estimate because some of those awards go for projects which have other components as well. [CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this figure to \$18 million for the record.]

We believe that fetal tissue research has great promise particularly in the treatment of certain diseases such as Parkinson's disease, diabetes, and others. We feel strongly that as long as firm ethical guidelines are followed and that Institutional Review Board regulations are complied with, for example, that there shall be no compensation for acquisition of fetal tissue, this research can be

done in an ethical manner. Because of the importance of the research, we feel strongly that it be pursued. We have heard no indication as yet that there is any intention to restrict us from carrying out such research. And the prohibitions on human embryo research that have been applied in this year do not apply to fetal tissue research.

GENE THERAPY RESEARCH

Mr. PORTER. I haven't heard specific plans in this area, but I wouldn't doubt that you might face that in the reauthorization process.

Last year you appointed an advisory panel to review NIH's support of gene therapy research. The panel concluded that although this field has great promise in the long run, early research has been over-sold and that NIH should shift its funding focus from premature clinical research to basic gene therapy research. How do you plan to enforce the greater emphasis on basic research within the institutes?

Dr. VARMUS. First of all, let me say that the impact of that report is already being felt in the news accounts I read of gene therapy. The public is becoming very rapidly aware that gene therapy, while a laudable goal and one that will be no doubt extremely important in medical care in the future, is not yet an established mode of treatment. There are no unqualified successes in this area as yet.

The institute directors who oversee research that bears on gene therapy—particularly with respect to the generation of delivery devices for genes, the cells that are especially important targets for gene therapy, and the regulation of such delivered genes—have all been asked to look very carefully at the report. I am going to be meeting with those institute directors about two weeks from now once the hearings are over to begin to consider how we go about achieving the goals that the Motulsky and Orkin panel has recommended.

I would point out to you that the majority of the so-called clinical trials that have been carried out in this area have not been paid for with NIH money. Most of them have been paid for by companies, carried out by investigators who are often supported by NIH grant money to do other kinds of things, at institutions that are NIH-supported. So we feel very involved in the process even when the research is actually paid for specifically by biotechnology or pharmaceutical companies. I will be asking institute directors to tell me how they plan to respond, and we'll try to work towards achieving what I think are ultimately tremendously beneficial goals through the use of gene therapy.

STRONG SUPPORT FOR NIH

Mr. PORTER. Dr. Varmus, you have been in the witness chair there now for about two hours and fifteen minutes. You've done an absolutely excellent job. I can't commend you enough not just for your testimony, but for the wonderful work that you do at NIH and the absolutely outstanding group of scientific leaders represented in this room and scientists represented at the institute that you have brought together.

I also would like to double your funds. I think it is perhaps the best investment we make anywhere in Government, and I think, frankly, we ought to very seriously plan on how we can double the funding or at least increase it very substantially. At one time toward the end of the Cold War, we all had a very strong feeling that we would be able to move money from defense needs into other priorities, and in my mind that meant moving a great deal more money into NIH. That has not happened and there are a lot of reasons for it. But I don't think that's any reason for us to simply sit still and say this is a tough budgetary environment and we can't do anything about that. I think we ought to set plans right now for how we can really make a very much stronger contribution in this area and work toward achieving that. I just can't think of any part of government that is doing a better job not only for the American people, but for humankind than NIH and all of the researchers that you have on campus and fund throughout our country. We just want to do everything we can to provide to you the kind of tools that you need, including the clinical center, I might say, to continue to do the fine work that you do.

We look forward to working together with you to that end. I think this is going to be a very, very difficult budgetary situation, far more difficult than last year, and every effort will be needed to make this happen. But we intend to do our best to make it happen.

Dr. VARMUS. I would be happy to work with you toward those goals. And, as you know, our admiration for what you've done for NIH this year and in the past is unbridled. I very much appreciate the leadership you have shown with this committee.

Mr. PORTER. Thank you, Dr. Varmus. Thank you all.

The subcommittee will stand in recess until 10:00 a.m. tomorrow.

[The following questions were submitted to be answered for the record:]

QUESTIONS SUBMITTED BY CONGRESSMAN PORTER

GRANT APPLICATION RESUBMISSION POLICY

Mr. Porter: In October, Science reported that NIH is considering a policy of limiting grant applications to one resubmission of a grant application, to address the problem that so much of the application pool is repeat applications. Have you made a final decision on this policy, and what reaction have you gotten from the extramural community.

Dr. Varmus: A growing proportion of applications are amended, and a growing number of awards are made to amended applications. These amended applications place a burden on the review process, and the amendment submission process, as it currently exists, delays the start of projects that eventually get funded. We have not yet limited the number of amended applications that may be submitted, but are considering doing so. If investigators have not been successful after the specified number of attempts on a given application, they would still have the option of coming in with a new and different application.

FULL TIME EQUIVALENT TARGETS

Mr. Porter: What are the main approaches you have used to meet your FTE targets under the President's downsizing plan?

Dr. Varmus: As we began the efforts to meet our FTE targets, the NIH first relied on "buyouts". Approximately 300 employees accepted buyouts, primarily in occupations, series and grades that had been identified for reductions, such as supervisors, employees in senior level positions, and employees in administrative occupations determined to be "headquarters" and "control" positions. With the ending of the buyout program, we have used the early retirement option, attrition and some limited hiring freezes to meet FTE reductions. As we continue streamlining and reengineering, we are looking to retrain employees when possible for new occupations at NIH. For those employees who perhaps are not interested in retraining we are offering career counseling and career transition services to provide them with the tools and skills necessary to find new positions or to assist them in developing strategies to continue work if they retire from the NIH.

Mr. Porter: Do you expect to be able to meet your lower target in 1998 and beyond with the steps already taken, or will further downsizing be required?

Dr. Varmus: We are hopeful that the steps that we have taken, and will continue to take, especially in the areas of early retirement, selective hiring freezes and career counseling and career transition, will enable us to meet our lower FTE targets for 1998 and beyond. However, we will continue to monitor our use of FTEs to ensure that reductions are taken where appropriate in accordance with mission and organizational needs.

ADMINISTRATIVE COSTS

Mr. Porter: The 1996 bill requires you to contain NIH administrative costs to levels 7.5 percent below 1995. How do you plan to curtail these costs?

Dr. Varmus: The FY 1996 Continuing Resolution requires a 7.5 percent reduction in the Research Management and Support (RMS) budget activity from the FY 1995 level.

The NIH is pursuing several strategies to achieve these reductions, including decreasing or eliminating overtime costs and not filling existing vacancies. Some Institutes Centers and Divisions (ICDs) have terminated non-permanent personnel, such as those in the Stay-in-School program and restricted promotions and employee bonuses. Of course, expenditures for supplies and equipment have been reduced as well. Travel, including travel for site visits to monitor and review grantee and contractor activity will be reduced. Several streamlining efforts are underway at the NIH to achieve greater efficiencies in management and operations. These streamlining efforts are heavily dependent on increased use of automation; however, reductions in the purchases of computer equipment and software have been necessary. Reductions in the RMS activity will require reductions in information dissemination activities. Development of the computer data base system and related data collection processes for clinical trials, alternative therapies, and rare disease research will be decreased as well.

Mr. Porter: Is it being managed centrally, or are you letting each Institute decide on its own approach?

Dr. Varmus: Each Institute was required to reduce its RMS activity by 7.5 percent; but, because NIH recognizes that the RMS activity contains a variety of functions which differ among ICDs, there was no consistent approach to exact the reductions centrally. Therefore, the NIH allowed each Institute to minimize administrative expenditures of lower priority or waning necessity and at the same time provide support to functions which are deemed essential to the accomplishment of its mission.

CONTRACTING OUT SERVICES

Mr. Porter: Are you considering more far-reaching issues, such as contracting out your computer services or some of the building and grounds personnel?

Dr. Varmus: At this time, there are no specific plans to contract out services in these areas.

FREDERICK CANCER RESEARCH AND DEVELOPMENT CENTER

Mr. Porter: The Bishop-Calabresi report on the Cancer Institute's intramural program recommended moving portions of the Frederick facility back to the Bethesda campus and converting its functions to a core program for all of NIH, not just National Cancer Institute (NCI). Do you plan to accept and implement this recommendation?

Dr. Varmus: The NCI is actively reviewing and implementing many of the recommendations made in the Bishop-Calabresi report which includes all the operations at the Frederick Cancer Research and Development Center (FCRDC). The Bishop-Calabresi report suggested that NCI relocate components of the FCRDC to Bethesda, in the following order of priority: a) all clinical and Laboratory components of the Biologic Response Modifiers Program (BRMP) [the production facility could remain at Frederick]; b) the remainder of the NCI Intramural laboratories; and c) ABL contract operations whenever feasible. Due to the complexities related to carrying out these recommendations, the NCI is carefully assessing each recommendation and developing appropriate strategies that not only address the concerns expressed in the report but also enhance and complement NCI's research mission.

At this point, NCI has reorganized FCRDC to more clearly define reporting responsibilities; to assure that the appropriate level of oversight is provided; and to address concerns relating to the separation of core services and the execution of research activities. The Deputy Director, NCI has been given responsibility for overseeing the entire FCRDC operation. The Scientific Coordinator (formally the Associate Director for FCRDC) reports directly to the Deputy Director, NCI. Additionally, the FCRDC Contracts Operation Section has been elevated to branch status with the branch chief reporting directly to the Associate Director for Extramural Management. All contract management and overall administrative management of the facility is now consolidated in one office with direct access to upper management.

All intramural research projects at the FCRDC, including the clinical and laboratory components of the Biologic Response Modifiers Program, have been reassigned functionally to the appropriate NCI Division to assure that research activities are integrated into the ongoing research activities of NCI intramural laboratories in Bethesda and that they undergo established scientific review. The BRMP clinical operation at FCRDC, which has been transferred to the Division of Clinical Sciences, is currently scheduled for a scientific review in September 1996. Specific recommendations for a programmatic configuration, emanating from that review process, will be submitted to NCI's Executive Committee for consideration. The NCI will seriously consider the recommendation of the site visit team and other review groups in developing future plans for FCRDC clinical and laboratory activities, including their geographic location.

Finally, the NCI is also restructuring existing processes to assure that there is a clear distinction between the provision of research support services and execution of intramural research. A revised process by which intramural and extramural scientists may request access to core research support services is under development. Core

services will include animal models, informatics/scientific computing, developmental therapeutics, development diagnostics, complex genetics, and production/fermentation. The availability of these invaluable research core services to cancer researchers not only nationwide but worldwide is consonant with the spirit and intent of the Bishop-Calabresi Report.

IMPACT OF EXTERNAL ADVISORS' RECOMMENDATIONS

Mr. Porter: As a result of the changes you are implementing in the overhaul of the intramural program recommended by the Marks-Cassell advisory panel, how many intramural labs have been de-funded or personnel reassigned?

Dr. Varmus: One of the most important recommendations of the External Advisory (Marks-Cassell) Committee was to improve the rigor of the external review process by strengthening the membership and function of the Boards of Scientific Counselors (BSCs) which review intramural research. Each Institute has a BSC which consists of senior extramural scientists who review each Laboratory/Branch at the NIH every four years. Thus, since the Marks-Cassell Committee recommendations were issued in April, 1994, approximately half of the Laboratories/Branches at the NIH have been reviewed by BSCs. Every Institute has had significant changes in resources assigned to specific individuals and in reassignment of individuals as a result of this review process. In some cases funds have been redirected to higher priority research within intramural research programs and in other cases funds have been shifted to extramural research. The largest of these shifts has occurred in the NCI where \$24.8 million has been redirected into extramural research project grants. In addition, many of our Institutes have new leadership either at the level of the Director of the Institute, or Scientific Director of the Intramural Program, or both, and there has been significant reorganization as a result of these leadership changes.

Some of the changes since issuance of the Marks-Cassell report are summarized below:

National Cancer Institute (NCI): Total reorganization, with elimination of at least one laboratory, changes in leadership in laboratories, and reassignment of resources, is in progress (new Director and Scientific Directors, new organization following the Bishop-Calabresi blue ribbon panel report on the NCI intramural program).

National Heart Lung Blood Institute (NHLBI): One major laboratory is being cut substantially and four other scientists have been reassigned.

National Institute of Dental Research (NIDR): New leadership is being sought for one major laboratory, and substantial re-organization of the intramural program is planned (new Director).

National Institute of Neurological Disorders and Stroke (NINDS): Two major laboratories are currently being cut substantially (new Director and Scientific Director).

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Seven principal investigators have been de-funded.

National Institute of Allergy and Infectious Diseases (NIAID): One principal investigator has been de-funded and three FTEs were reassigned (new Scientific Director).

National Institute of Child Health and Human Development (NICHD): Downsizing of one major laboratory.

National Eye Institute (NEI): Plans are underway to substantially downsize four laboratories based on BSC reviews.

National Institute of Mental Health (NIMH): Two major laboratories are being closed and one laboratory is being downsized (new Director and review of intramural research program is underway).

National Institute of Drug Abuse (NIDA): Major reorganization expected (new Director and Scientific Director).

National Institute on Alcohol Abuse and Alcoholism (NIAAA): One major laboratory closed, four FTEs reassigned.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): No major changes yet, but review of intramural program is planned (new Director).

National Institute on Aging (NIA): Ten principal investigators have been reassigned or significantly defunded.

National Center for Human Genome Research (NCHGR) and National Institute on Deafness and Other Communication Disorders (NIDCD) have relatively new intramural programs and are carefully building these programs under the leadership of new Scientific Directors in response to advice from their Boards of Scientific Counselors.

INTRAMURAL PROGRAM REVIEWS

Mr. Porter: Which Institutes are slated for the next review of their intramural program?

Dr. Varmus: A review of NIMH is underway, with an outstanding group of extramural researchers chaired by Dr. Herbert Pardes, Dean of the Faculty of

Medicine, Columbia University College of Physicians and Surgeons. The review committee has met twice.

Reviews of National Institute of Drug Abuse, National Institute of Aging, and National Institute of Arthritis and Musculoskeletal and Skin Diseases are in the planning stage and should be initiated by this summer.

NATIONAL INSTITUTES OF HEALTH AUTHORIZATION

Mr. Porter: What are the most significant changes to the NIH authorization statute you intend to recommend to Congress?

Dr. Varmus: The following are the most significant changes to the NIH authorization statute that NIH intends to recommend to the Congress.

PROGRAMS TO BE REAUTHORIZED

Reauthorization of Appropriations for NIAAA--Extend the authorization of appropriations for the National Institute on Alcohol Abuse and Alcoholism for five years through FY 2001.

Reauthorization of Appropriations for NIA--Extend the authorization of appropriations for the National Institute on Aging for five years through FY 2001.

Extension of Appropriations--Extend the authorization of appropriations for the Public Health Service Act, Section 409A, for the expansion and intensification of research on osteoporosis, Paget's disease, and related bone disorders for five years through FY 2001.

Reauthorization of Appropriations for NCI--Extend the authorization of appropriations for the National Cancer Institute for five years through FY 2001.

Reauthorization of Appropriations for NIDA--Extend the authorization of appropriations for the National Institute on Drug Abuse for five years through FY 2001.

Reauthorization of NICHD Contraception & Infertility Centers--Extend the authorization of appropriations for the National Institute of Child Health and Human Development research centers with respect to contraception and infertility for five years through FY 2001.

Reauthorization of Appropriations for NHLBI--Extend the authorization of appropriations for the National Heart, Lung, and Blood Institute for five years through FY 2001.

Reauthorization of Appropriations for NLM--Extend the authorization of appropriations for the National Library of Medicine for five years through FY 2001.

Reauthorization of Appropriations for NIMH--Extend the authorization for appropriations for the National Institute of Mental Health through FY 2001.

Reauthorization of Comprehensive Plan for AIDS Research--Reauthorize the Comprehensive Plan, Bypass Budget and Consolidated Appropriation of the Office of AIDS Research (OAR) through FY 2001.

Reauthorization of OAR's Emergency Discretionary Fund--Reauthorize the Office of AIDS Research Emergency Discretionary Fund through FY 2001.

Reauthorization of Appropriations for the National Research Service Awards Program--Reauthorize the appropriations authority for five years through FY 2001.

Reauthorization of the Discretionary Fund of the Director of the NIH--Reauthorize the Discretionary Fund for five years through FY 2001.

Reauthorization of Appropriations for Modernization and Construction of Biomedical and Behavioral Research Facilities--Reauthorize the appropriations authority for modernization and construction of biomedical and behavioral research facilities for an additional five years and modify percentages of Federal support to 40 percent of the cost of the total facility, or 30 percent of the cost of the part of the facility that is proportionate to the use of the facility.

Reauthorization of Appropriations for the Construction of Regional Primate Research Centers--Reauthorize the appropriations authority for the construction of regional primate research centers for an additional five years through FY 2001 and change the language in Section 481B to replace "shall" with "may."

Reauthorize AIDS Research Loan Repayment Program--Reauthorize the NIH AIDS Research Loan Repayment Program for five years through FY 2001.

PROPOSALS TO ENHANCE NIH EFFICIENCY AND FLEXIBILITY

Provide Authorities of the Research Institutes to the NIH Director--Provide the authorities of the National Research Institutes to the NIH Director so that they may be delegated to the NIH Entities as the NIH Director deems appropriate.

Breast and Prostate Cancer Plans--Delete requirements for developing and submitting to Congress breast and prostate cancer research plans.

Repeal Obsolete Committees--Eliminate certain advisory committees that no longer carry out the purposes for which they were established.

Council Review Threshold--Increase from \$50,000 to \$100,000 per annum the direct cost dollar amount for grant and cooperative agreement awards that can be made after scientific and technical peer review but without Council recommendation, and extend this provision to the other agencies of the NIH.

Frequency of Advisory Council/Committee Meetings--Eliminate requirements for frequency of national advisory council/committee meetings.

Reports Elimination--Eliminate mandated research and progress reports submitted by the Director of the NIH and the NIH ICDs.

Eliminate Earmarks--Amend NIH statutory authorities by eliminating the specific earmarks for an elderly research center funded by NIAAA and the numerical designation of six centers for breast cancer research and six centers for prostate cancer research (specialized programs of research excellence--SPOREs) funded by NCI.

TRAINING/LOAN REPAYMENT PROPOSALS

Expansion of intramural research training authority--Amend Sec. 402(b)(1) of the PHS Act to give the Director, NIH, the authority to establish intramural research training programs at NIH for deserving graduate, pre-doctoral, and post-doctoral candidates.

Extend NHSC Loan Repayment Provisions to the NIH Loan Repayment Programs--Provide the same maximum yearly financial benefits to the Loan Repayment Programs (LRP) of the NIH that now apply to the National Health Service Corps Loan Repayment Program (NHSCLRP).

PERSONNEL PROPOSAL

Amend Retirement Provision of SBRS--Amend the retirement provisions of the Senior Biomedical Research Service to enable the Secretary to make a contribution as a non-profit entity to the academic retirement systems in which members participated immediately prior to their appointment in the Service.

CONFIDENTIALITY PROPOSAL

Confidentiality of Baby-Donors of Cord Blood--Amend PHS Act to protect privacy and confidentiality for baby-donors of cord blood used in transplantation.

TECHNICAL PROPOSALS

Construction Definition--Insert the definition of construction that appeared in the PHS Act "Health Law," as amended, into NIAAA's current PHS Act Section.

Advisory Panel on Studies of Malnutrition in the Elderly--Repeal Section 1902 of the NIH Revitalization Act of 1993 requiring the establishment of an advisory panel to oversee the design, implementation and evaluation of two studies relating to malnutrition in the elderly and include this proposal in the Omnibus bill "Federal Advisory Committee Termination Act" to delete the requirement for this committee.

Construction Cross-Reference--Correct obsolete cross-reference to construction definition in NIDA's multi-disciplinary centers authority.

HEALTH SERVICES RESEARCH

Mr. Porter: What is your view of NIH supporting health services research?

Dr. Varmus: The NIH is firmly committed to, and has an established tradition of, supporting health services research. It has been a prime supporter and progenitor of the growth and development of this field. In fact, this investigative arena represents an integral component of the NIH research portfolio, and is funded principally by the three former ADAMHA Institutes (NIAAA, NIMH and NIDA). It comprises a key element in the research continuum, beginning with fundamental research and proceeding to patient-oriented treatment and prevention research. Approaches, tested in the laboratory and then through experimental, clinical research, are taken to the next step and evaluated in real world settings.

Mr. Porter: The three former ADAMHA institutes have a statutory mandate to fund services research, and other Institutes do so as well, but are these activities more appropriate for the Agency for Health Care Policy and Research?

Dr. Varmus: Health services research includes studying issues of financing, economics and treatment outcomes. The knowledge gained from health services research subsequently informs and is integrated into ongoing and future laboratory and patient-oriented studies. Furthermore, health services cannot be understood separately from clinical medicine; services research must be carefully coordinated with clinical research to gain the synergy necessary for successful treatment. This coordination can only be achieved within the same agency. To move this integral aspect of research from the research continuum would significantly weaken NIH's programmatic activities.

Mr. Porter: Would you recommend that the services research set-aside for the three ADAMHA institutes be repealed in the NIH re-authorization?

Dr. Varmus: NIH is opposed to all set-asides or earmarking of funds. The agency has a long-standing tradition in health services research and is firmly committed to its support. This area of investigation is a vital component of our research portfolio, in that approaches tested in the laboratory and then through experimental, clinical research are taken to the next step in the research continuum and evaluated in a real world setting. Knowledge gained from health services research subsequently informs and is integrated into ongoing and future laboratory and patient-oriented studies.

HUMAN EMBRYO RESEARCH

Mr. Porter: Do you have plans to follow up on the recommendations of your advisory committee on human embryo research by establishing ground rules for such research if the ban were to be lifted next year?

Dr. Varmus: The NIH began last year to develop plans to establish the advisory committee recommended by the Human Embryo Research Panel and the Advisory Committee to the Director for the review of those proposals that would have been permitted under the President's directive. One of the committee's first tasks would have been to finalize the stringent guidelines recommended by the panel for the funding, review, and conduct of research. The committee also would have an important role in advising NIH about how to enhance public understanding of the nature of research involving human in-vitro fertilization and the preimplantation embryo and in monitoring ethical and scientific issues associated with this research on a continuing basis.

DEPARTMENT OF DEFENSE FUNDING

Mr. Porter: Philosophically, do you feel that the Department of Defense should be funding biomedical research in areas such as breast and prostate cancer and osteoporosis?

Dr. Varmus: Advances in human health, including advances in breast cancer, prostate cancer, and osteoporosis, come about through the support of those research projects judged to be of the highest merit, independent of the source of funding. As the number of meritorious investigators working in a particular field grows, the probability for scientific advances increases--irrespective of whether the research is funded by NIH or another Federal agency such as the Department of Defense.

We would point out, however, that the National Cancer Institute (NCI) is the principal agency of the Federal government responsible for conducting and coordinating efforts in cancer research, including breast and prostate cancer; and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has the lead in addressing bone disease research, including research on osteoporosis. As NIH components, these Institutes have an advantage in being able to work closely with the other Institutes in addressing the many dimensions of cancer and osteoporosis. Coordination of this kind among Institutes and across agencies is critical to making progress against these diseases.

INFORMATION DISSEMINATION

Mr. Porter: You sent us a report last October outlining your plans to enhance NIH information dissemination. The report described possible options that were going to be further studied by working groups. What changes have taken place since the report was transmitted last fall?

Dr. Varmus: NIH has substantially enhanced its communications programs since its January 1995 communications conference involving outside experts and NIH staff, and the subsequent report to the Appropriations Subcommittee in October 1995. Many changes, which are being implemented through working groups of NIH communications staff, have already been made; other recommendations are still being developed and considered. These include:

- Two pilot programs of *Health Week*, developed in conjunction with Maryland Public Television (MPT), have been completed, focus tested, and aired. MPT is evaluating whether private sector funding can be obtained to continue this series.
- The NIH Home Page on the Internet has blossomed with useful information for many NIH audiences. This new mode of communications for NIH is constantly being updated, enhanced, and made more useful to the public. By Fall of 1996, the Home Page will include a body of 110 NIH "best selling" brochures about health prepared specifically for the public and patients.
- A strategic plan for NIH communications has been drafted, spelling out communications objectives, target audiences, key concepts to convey, strategies and tactics. This strategic plan will guide all of NIH's institutes and divisions, thereby strengthening NIH's overall information dissemination efforts.
- A series of recommendations have been made by a working group focused on public understanding of NIH and biomedical research. These recommendations include specific projects conveying important health information to smaller media markets around the country, thereby reaching a wider audience; enlisting NIH grantees and advisory council members to improve public understanding of the importance and benefits of biomedical research around the country; creating a traveling exhibit with important health and science information aimed at the public; and piloting a weekly news advisory aimed at bringing important health science news to a larger share of the public.
- A feasibility study, including a survey, has been completed to review NIH's responsiveness to the approximately 2 million public inquiries (many of them from patients or their families) received annually via telephone. One interesting finding of the survey was that, for the most part, incoming callers were being directed expeditiously to the proper NIH office for assistance. Recommendations for improved access via telephone will soon be presented to the NIH Director for consideration.
- Means have been developed to streamline NIH's outreach and response to the mass media, an important source for the public of current health information. These include a centralized fax systems used by all institutes and divisions, centralized access to NIH press releases and reports via on-line technology, and training for scientists about working effectively with reporters.

PUBLIC INFORMATION OFFICES

Mr. Porter: Have you reached a decision on whether to centralize public information offices?

Dr. Varmus: Although NIH has decided not to centralize public information offices, we have centralized a number of activities, projects and management systems in order to be more effective and efficient and to gain cost savings. For example, we have now consolidated fax lists important to all NIH components under a single contract in order to gain savings in cost and human resources. Other centralized contracts have been established for example for online communications--to avoid duplication throughout the institutes, centers and divisions (ICDs). This has brought small cost savings as well. Certain other health education projects valuable to all the ICDs in reaching special audiences are being managed centrally--for example, the NIH Radio News Service (reaching more than 500 radio stations a week with health information)--to avoid duplication in the individual components, thus conserving money and human resources. Since the January 1995 communications conference, more cooperative, centralized planning is occurring at NIH in the areas of health communications. For example, an NIH strategic communications plan has been drafted that will help streamline and harmonize the efforts of the various NIH components with significant health education and information programs. One of the working groups formed after the January 1995 communications conference, the Shared Resources Working Group, is still looking into additional consolidation of projects and activities with an eye toward cost savings, human resource conservation, and increased efficiency.

RELEASE OF NATIONAL INSTITUTES OF HEALTH RESEARCH DATA

Mr. Porter: State for the record the NIH policy on release of data generated in research supported by NIH. If you are not at liberty to release data, even though it is publicly funded, how do peer-reviewed journals and others validate the data.

Answer: Data that are produced on NIH research grants are the property of the grantee institution, consistent with the principle that the awards are made as assistance in support of the investigator's research. However, NIH does have policies that encourage the sharing of all data produced under grants, especially materials that are considered to be unique biological resources, such as cell lines, crystallography coordinates, and nucleic acid sequence data. Investigators are asked to place these unique resources in national repositories so that they are easily available to all interested investigators. Research produced under NIH contracts is the property of the government, and publication is covered under the rights and data clauses within the specific contract.

Data generated by intramural NIH scientists or within NIH facilities are considered the property of the U.S. Government. They are disseminated to the public through publication in peer-reviewed scientific journals. Publication may be slightly delayed in certain situations where a patent application is involved. Once published, it is NIH policy that the data or materials be shared, as appropriate and feasible, with other researchers.

Peer reviewed journals do not validate data per se; however, if they have serious reservations about the validity of the data, they would most likely request that

the investigator provide additional information or some form of independent verification. Should there be some concern about data validation for work produced under an NIH contract, NIH could review and verify these data.

The data become validated principally through subsequent replication by other scientists, who thereby confirm the results and to apply the techniques to their own lines of investigation. If there are then questions about the validity of the data or the reproducibility of the results, these issues are typically addressed in the scientific literature. In addition, the Scientific Directors of the various ICD intramural programs and the academic institutions in which grantees work are responsible for overseeing the integrity of the process by which data are accumulated, and for defending this process if it is questioned.

RECOMMENDATION TO THE NATIONAL CENTER ON SLEEP DISORDERS

Mr. Porter: Dr. Varmus, now that the Advisory Board to the National Center on Sleep Disorders Research has finished its research plan and you have approved it, how do you plan to move forward to ensure that the plan's recommendations are implemented?

Dr. Varmus: The first steps to implement the research plan are being taken already. The National Center on Sleep Disorders Research (NCSDR) has begun wide distribution of the plan in the research community, which is expected to draw the attention of researchers to the scientific questions that need to be answered. The Institutes supporting sleep related research are identifying ways to strengthen their current sleep portfolios. For example, support for sleep related research across NIH is estimated to increase from \$72.8 million in FY 1995 to \$79.3 million in FY 1997. Also, at least one Institute has designated sleep related grants near the payline as grants with high program relevance thereby assuring that they will be funded.

The Sleep Disorders Research Advisory Board, the trans-NIH Sleep Coordinating Committee, and the NCSDR are working together to stimulate new activities in the following areas:

- Basic research on the fundamental molecular and cellular processes underlying sleep.
- Patient oriented research to improve the diagnosis and treatment of sleep disorders
- Applied research to evaluate the scope and consequences of sleepiness
- Training a new cadre of scientists and health care providers to study and treat sleep problems.

REVIEW OF UROLOGY RESEARCH GRANTS

Mr. Porter: There is concern among some in the outside community about the manner in which urology research grants are reviewed at NIH. What steps are you taking to reduce the number of study sections that review urology grant applications and to improve the level of urology expertise on these study sections?

Dr. Varmus: In order to relieve concern among some in the outside community regarding the manner in which some urology research grant applications are reviewed at NIH, the Division of Research Grants (DRG) is aggregating applications in a single review group when appropriate, and will increase the number of reviewers with specific urological expertise in cases where this cannot be done.

1. DRG is conducting a pilot study beginning with the upcoming review round in June 1996. A Special Emphasis Panel (SEP) is being established to review urology applications, with an emphasis on interstitial cystitis. Applications that would have gone to several study sections (e.g., General Medicine B & Surgery, Anesthesiology and Trauma) are being assigned to this SEP whose membership will reflect strong urological expertise. This desirable approach to review has been facilitated by an increased number of applications from investigators in certain areas of urology.

2. In other areas of urology research where the application workload is small, but where the expertise needed is too diverse to be included in the aforementioned SEP, this approach will not work as easily. Therefore, we are planning to coalesce these applications for assignment to fewer study sections and add additional urological expertise to those study sections. We are prepared to utilize the "flexible" appointments of certain study section members for less than the usual three meetings per year, as fluctuating workloads dictate.

COMPETING RESEARCH GRANTS BY INSTITUTE

Mr. Porter: Provide for the record a five-year table indicating the percentage of research grants that were awarded in response to an RFA by Institute.

Dr. Varmus: The information provided below is for all of NIH rather than by institute. Responses to Requests for Applications (RFAs) can be funded by institutes other than those which initiated them; therefore the overall NIH figures given below are more precise.

Percentage of Research Project Grants Awarded in Response to RFAs FY 1991-1995			
FY	Competing RPGs	RFAs Awarded	Percent of Total
91	6,462	506	7.8
92	6,768	487	7.2
93	6,149	560	9.1
94	6,474	843	13.0
95	6,579	641	9.5

FISCAL YEAR 1997 NIH AREAS OF EMPHASIS

Mr. Porter: Provide a crosswalk table showing the requested FY97 funding increases by area of special emphasis by Institute.

Dr. Varmus: The following table shows the special emphasis areas for the FY 1997 Director's increases:

National Institutes of Health

Special Emphasis Areas
FY 1997 Director's Increases
(Dollars in thousands)

	Biology of Brain Disorders	Pathogenesis	Preventive Strategies	Genetics of Medicine	Advanced Instrumentation	Total
NCI	—	\$5,000	\$4,000	\$5,000	\$3,000	\$17,000
NHLBI	\$1,000	3,000	2,000	2,000	2,000	10,000
NIDR	1,000	1,000	—	—	—	2,000
NIDDK	—	—	4,000	2,000	—	6,000
NINDS	5,000	—	—	2,000	—	7,000
NIAD	—	3,000	2,000	—	—	5,000
NIGMS	—	2,000	—	2,000	2,000	6,000
NICHD	1,000	1,000	2,000	—	—	4,000
NEI	2,000	—	—	—	—	2,000
NIEHS	1,000	1,000	2,000	—	—	4,000
NIA	3,000	2,000	—	—	—	5,000
NIAMS	—	2,000	—	—	—	2,000
NIDCD	1,500	—	1,000	—	—	2,500
NIMH	3,000	—	2,000	—	—	5,000
NIDA	2,000	—	2,000	—	—	4,000
NIAAA	1,000	—	500	500	—	2,000
NINR	500	—	—	—	—	500
NCRR	—	—	—	2,000	2,000	4,000
NCHGR	—	500	1,000	5,500	—	7,000
FIC	—	—	—	—	—	—
NLM	—	—	—	—	4,000	4,000
TOTAL	22,000	20,500	22,500	21,000	13,000	99,000

RECOMMENDED FUNDING LEVELS FOR GRANTS

Mr. Porter: With the understanding that reductions are not done by formula, please provide a table showing by Institute the estimated average reduction in research project grant awards from the Council-approved level for FY 1995-1997.

Dr. Varmus: Although an overall rate of reduction for research project grants (RPGs) can be calculated using a simple comparison of initial review group recommended levels to awarded levels, this would not accurately reflect grant funding situations. NIH now uses policies outlined in "A Plan for Managing the Costs of Biomedical Research," the NIH Cost Management Plan (CMP), in funding RPGs. Before the CMP was developed, Institutes' funding policies typically called for across-the-board reductions of specified percents below recommended levels in order to support a targeted number of grants. In that situation, reporting the percents of downward negotiations was clearly meaningful. Now, as suggested by the Committee, the CMP directs Institutes to utilize various strategies to manage increases in grant costs in order to achieve an average cost increase which does not exceed the amount of the Biomedical Research and Development Price Index (BRDPI) over the previous year. Recommended strategies include consideration of the costs of grants of equal merit in selecting grants for funding and negotiations of individual grants, if necessary, to ensure that the average cost increases of each Institute's RPG portfolio do not exceed CMP guidelines. Formulaic reductions are not acceptable as NIH developed its current policies. The CMP directs that NIH replace formulaic across-the-board downward negotiations with rational scientific and administrative choices as NIH's grant funding strategy.

FISCAL YEAR 1997 BUDGET REQUEST

Mr. Porter: Provide a "who struck John" table identifying the FY 1997 NIH request by Institute at each stage of the budget formulation process.

Dr. Varmus: The following tables identifies the FY 1997 NIH request at each stage of the budget formulation process. The NIH professional judgment budget and the submission to DHHS were provided in the NIH aggregate.

DHHS-National Institutes of Health

Chronology of FY 1997 President's Budget
(Dollars in thousands)

	Fiscal Year 1997				
	FY 1996 Estimate	NIH Prof. Jud. Budget	PHS to DHHS	DHHS to OMB *	President's Budget **
NCI	\$2,025,294	This level	This level	\$2,040,479	\$2,060,392
NHLBI	1,297,941	was not	was not	1,308,002	1,320,555
NIDR	170,887	developed	developed	172,829	174,463
NIDDK	759,517	by ICD.	by ICD.	765,866	772,975
NINDS	657,727			664,836	671,148
NIAID	573,610			570,592	584,362
NIGMS	920,836			927,090	936,573
NICHHD	534,449			537,954	543,441
NEI	305,060			307,137	310,072
NIHHS	282,847			286,953	289,114
NIA	452,132			457,412	461,541
NIAMS	238,789			240,908	243,169
NIDCD	174,852			177,447	179,090
NIMH	567,737			571,836	578,149
NIDA	305,110			307,153	312,014
NIAAAA	188,472			190,457	192,280
NINR	50,935			51,400	51,951
NCRR	321,969			316,090	309,344
NCHGR	169,041			176,142	177,788
FIC	15,654			15,493	15,790
OAR	1,407,824			1,450,068	1,431,908
NLM	138,277			140,443	143,268
OD	233,890			230,479	226,913
Subtotal	11,792,850			11,907,066	11,986,300
B&F	146,151			210,000	420,000
Total, NI	11,939,001	\$13,036,098	\$12,246,393	12,117,066	12,406,300

* The base for this level was the FY 1996 President's Budget of \$11,764,066.

** The base for this level was FY 1996 Congressional Action of \$11,939,001.

ALTERNATIVE MEDICINE RESEARCH

Mr. Porter: Provide a table indicating projected spending on alternative medicine research by Institute for FY 96.

Dr. Varmus: The following table provides preliminary projected spending on alternative medicine by Institute for FY 1996. It is expected that a better estimate will be available shortly.

ALTERNATIVE MEDICINE RESEARCH (Dollars in thousands)

	FY 1996 <u>Estimate</u>
NCI	\$ 296
NHLBI	1,075
NIDR	1,596
NINDS	500
NICHD	1,700
NIMH	357
NIAAA	262
NCRR	746
NINR	1,450
OD	6,430
TOTAL	\$14,412

RESOURCES FOR INTRAMURAL LABORATORIES/BRANCHES

Mr. Porter: Identify the average FTE size and cost of an intramural laboratory by Institute for FY 1990 and FY1995.

Dr. Varmus: At the time of the Marks-Cassell report in 1992, a complete summary of FTEs and budget assigned to the intramural research program was completed. This information, as well as the most recent 1995 data, are included in the attached Table. Since many of our intramural programs have undergone reorganization, with changes in the number of intramural Laboratories/Branches, it would be difficult to compare average cost or FTE per laboratory in 1992 with the current situation, so total FTEs, budget, and numbers of intramural Laboratories/Branches for each institute are given in the following table. Due to the tremendous variation in mission and research programs supported in NIH intramural labs, calculations of average costs and FTE size for laboratories do not provide a meaningful standard for making comparisons between institutes.

FTEs AND BUDGET FOR INTRAMURAL LABORATORIES/BRANCHES

1990 data are not readily available, but 1992 data were assembled for the External Advisory (Marks-Cassell) Committee.

<u>Institute</u>		<u>IRP FTEs</u>	<u>IRP Budget (\$millions)</u>	<u>Labs/Branches</u>
NCI	1992	1,854	\$360	50
	1995	1,571	373	55
NHLBI	1992	438	97	17
	1995	376	99	18
NIDR	1992	270	31	8
	1995	235	33	8
NINDS	1992	517	76	20
	1995	462	76	22
NIDDK	1992	457	80	21
	1995	399	84	21
NIAID	1992	653	120	16
	1995	582	131	17
NICHD	1992	346	68	16
	1995	303	76	18
NEI	1992	192	29	7
	1995	174	30	9
NIEHS	1992	631	71	17
	1995	549	72	14
NIA	1992	281	37	9
	1995	265	38	9
NIAMS	1992	82	16	4
	1995	68	19	4
NIDCD	1992	38	8	3
	1995	45	11	7
NIMH	1992	613	93	21
	1995	530	93	24
NIDA	1992	122	24	1
	1995	112	25	8
NIAAA	1992	106	20	5
	1995	93	21	4

NINR	1992	7	1	2
	1995	8	1	3
NCHGR	1995	116	40	6
TOTAL	1992	6,607	1,131	217
	1995	5,888	1,222	247
(% Change)		(-10.8)	(+8.0)	(+13.8)

1992 Funding/Lab & Branch = \$5.2 million

1995 Funding/Lab & Branch = \$4.9 million

(% change) (-5.8)

1992 FTE/Lab & Branch = 30.4

1995 FTE/Lab & Branch = 23.8

(% change) (-21.7)

SPENDING BY DISEASE

Mr. Porter: Provide the traditional one-pager identifying spending across NIH by major disease areas for FY 95-97. Include cardiovascular disease in the analysis.

Dr. Varmus: The following table identifies NIH spending by disease areas.

DHHS-National Institutes of Health Research Initiatives/Programs of Interest (Dollars in thousands)				
Research/Disease Area	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate	Percent Change
1. Aging	\$820,187	\$859,082	\$875,521	1.91
2. Alzheimer's Disease	296,741	308,717	314,159	1.76
3. AIDS Research	1,333,380	1,407,824	1,431,908	1.71
Minority AIDS Research	255,488	265,430	267,354	0.72
Pediatric AIDS Research	161,794	166,027	163,267	-1.66
4. Arthritis	207,310	218,094	221,269	1.46
5. Batten's Disease	2,481	2,605	2,663	2.23
6. Biotechnology Research	4,598,065	4,820,381	4,903,645	1.73
7. Cancer Research	2,434,304	2,576,781	2,612,819	1.40
Breast Cancer	363,870	403,273	409,545	1.56
Cervical Cancer	53,882	55,735	56,689	1.71
Lung Cancer	123,237	126,742	130,430	2.91
Ovarian Cancer	39,095	40,382	41,322	2.33
Prostate Cancer	85,465	92,982	94,614	1.76
Colo-Rectal Cancer	102,371	105,561	108,364	2.66
Uterine Cancer	13,649	14,159	14,450	2.06
8. Cardiovascular Research	948,859	997,190	1,015,154	1.80
9. Clinical Trials	1,172,633	1,213,350	1,224,746	0.94
10. Contraception/Reproduction Research	171,036	178,780	181,737	1.65
11. Cystic Fibrosis	58,645	61,032	62,056	1.68
12. Diabetes	295,142	309,641	313,334	1.19
13. Diagnostic Radiology	195,434	205,448	211,677	3.03
14. Diethylstilbestrol (DES)	7,844	8,065	8,252	2.32
15. Epstein Barr Virus (Chronic Fatigue)	17,560 8,020	18,428 7,700	18,620 7,818	1.04 1.53
16. Gene Mapping	659,016	702,015	718,959	2.41
17. Gene Therapy	191,458	200,747	204,748	1.99
18. Head Injury	54,183	56,874	57,950	1.89
19. Health & Behavioral Research	809,177	840,373	854,749	1.71
20. Fetal Tissue Research	23,693	24,826	25,293	1.88
21. Hypertension	170,334	176,680	179,445	1.56
22. Immunology	1,046,381	1,092,233	1,108,272	1.47
23. Infant Mortality/ (LBW)	327,108	341,217	347,136	1.73
24. Interstitial Cystitis	8,918	9,000	9,100	1.11
25. Kidney Disease	192,196	200,938	203,677	1.36
26. Lead Poisoning	20,869	21,331	21,442	0.52
27. Lupus	31,162	32,683	33,380	2.13
28. Lyme Disease	13,447	14,026	14,313	2.05
29. Nutrition Research	409,685	431,317	438,734	1.72
30. Obesity	87,398	91,905	93,707	1.96
31. Osteoporosis	103,660	108,550	110,803	2.08
32. Pertussis Vaccine	6,004	6,274	6,393	1.90
33. Prevention (NCI Primary Prev.)	2,872,909 436,999	3,031,801 458,534	3,092,695 463,119	2.01 1.00
34. Rehabilitation	156,870	166,734	169,801	1.84
35. Rural Health	95,546	99,563	101,808	2.25
36. Schizophrenia	112,016	118,511	120,681	1.83
37. Sexually Trans. Diseases/Herpes	105,372	110,019	111,839	1.65
38. Sickle Cell Disease	53,948	55,765	56,719	1.71
39. Sleep Disorders	72,489	76,000	77,294	1.70
40. Smoking and Health	125,712	132,297	135,214	2.20
41. Stroke	114,296	119,450	121,543	1.75
42. Sudden Infant Death Syndrome	43,752	46,064	46,821	1.64
43. Topical Microbicides	21,344	23,200	23,844	2.78
44. Tropical Diseases	59,399	61,776	62,966	1.93
45. Tuberculosis Research	61,981	64,021	64,972	1.49
46. Urologic Diseases	199,320	214,946	217,036	0.97
47. Vaccine Development Vaccine Related	273,174 299,750	285,960 314,426	297,045 325,791	3.88 3.61
48. Women's Health Research	1,632,205	1,725,236	1,753,096	1.61

SUCCESS RATES FOR SBIR GRANTS

Mr. Porter: What is the success rate for SBIR grants in Phase I, II and III?

Dr. Varmus: The attached table displays success rate for Small Business Innovative Research (SBIR) grants for FY 1995.

National Institutes of Health Small Business Innovative Research Success Rates FY 1995	
Type	Success Rate
Phase I (R43)	20%
Phase II (R44)	39%

The National Institutes of Health (NIH) does not fund Phase III SBIR development nor does the law require this. The objective of Phase III is for the small business concern to pursue with non-federal funds the commercialization of the results of the research or Research & Development (R&D) funded in Phases I and II. In some federal agencies, Phase III may involve follow-on non-SBIR funded R&D or production contracts for products or processes intended for use by the United States government.

LICENSES AND CRADAs

Mr. Porter: How many licenses and CRADAs does NIH have?

Dr. Varmus: The number of licenses and Cooperative Research and Development Awards (CRADAs) are as follows:

National Institutes of Health Licenses and CRADAs

FY 1985 - FY 1995

Executed Licenses	713
Executed CRADAs	269

Mr. Porter: How much is generated in royalties each year?

Dr. Varmus: In 1995, a total of \$19,388,000 in royalties were collected. Between FY 87 - FY 95 NIH collected a total of \$94,958,000 in royalty income.

Mr. Porter: How much of that goes back to NIH?

Dr. Varmus: All the funds, with the exception of a portion of the royalties from the AIDS Test Kit, go to NIH. Under the terms of the settlement with the Secretary, HHS and the Pasteur Institute, 80 percent of the test-kit royalties are turned over to the French-American AIDS Foundation. In 1995, the AIDS Test Kit earned \$4.6 million in royalties, of which \$3.68 million went to this foundation.

SERVICE CENTERS

Mr. Porter: How many service centers have been established at NIH?

Dr. Varmus: The competitive Service Center program was initiated by the NIH in order to facilitate the provision of administration and research support services in more efficient ways while still maintaining their high quality. Under this program, Institutes with established expertise and resources in particular areas offer these services to other Institutes for a fixed fee and arrangements are made between the parties based upon their mutual needs and interests. These arrangements are evaluated and reassessed on a periodic basis. Thirteen Centers were approved by the Director, NIH, on advice from senior staff for implementation in the fall of 1995. With the approval of one further center in March 1996, there are currently 14 Centers operational in the following 9 service areas: technology transfer, grants management, research training payback, committee management, procurement and contract activities, computer network support, database management, patient recruitment and travel, and personnel activities. Twenty-two of NIH's ICDs are participating as either providers or users of Competitive Service Centers.

Mr. Porter: How many Institutes currently use each service center established?

Dr. Varmus: Ten different ICDs participate as service providers and operate one or more service centers. In several service areas, multiple Centers are available to provide services to other Institutes, while in others only one Center is currently available. Twenty organizations at NIH are currently using one or more centers to obtain necessary support services that would otherwise need to be provided with more costly internal Institute resources. The number of Institutes using a particular Center varies, and currently ranges from one to seven.

Mr. Porter: What FTE savings is associated with the service centers?

Dr. Varmus: At the time of their implementations, NIH estimated that the establishment of Service Centers would result in a net savings to the NIH of 15 FTEs that could be redirected to research activities. A formal evaluation of this new program is due to take place one year after implementation and will provide more definitive information about savings to the ICDs involved and the success of these centers.

BIOMEDICAL RESEARCH AND DEVELOPMENT

Mr. Porter: Please indicate the estimated Biomedical Research and Development Price Index (BRDPI) for the FY 97 budget, and the projections for FY 98-01.

Dr. Varmus: The attached table displays the calculated Biomedical Research and Development Price Index (BRDPI) for FY 1997 - FY 01.

National Institutes of Health Biomedical Research and Development Price Index FY 1997 - FY 2001				
FY 1997	FY 1998	FY 1999	FY 2000	FY 2001
3.7%	3.7%	3.7%	3.7%	3.7%

ISSUES RELATED TO THE R0-1 APPLICATION

Mr. Porter: What percentage of R0-1 grants awarded were resubmissions in FY 91-95?

Dr. Varmus: For the five year period from 1991 through 1995, 40.7 percent of grants awarded were resubmissions. By individual year, the percentages are as follows:

1991	39.7%
1992	39.1%
1993	38.6%
1994	45.3%
1995	44.2%

NO COST GRANT EXTENSIONS IN FISCAL YEAR 1995

Mr. Porter: How many grants received no-cost extensions in FY 1995?

Dr. Varmus: We estimate that 3,700 research project grants received no-cost extensions in 1995.

SENIOR BIOMEDICAL RESEARCH SERVICE

Mr. Porter: How many Senior Biomedical Research Service positions have been allotted to NIH?

Dr. Varmus: Sixty Senior Biomedical Service positions have been allocated by HHS to NIH.

Mr. Porter: How are they allocated by Institute?

Dr. Varmus: Senior Biomedical Research Service appointments are granted individually by the Director, NIH, to outstanding research scientists, and are not allocated on the basis of organizational structure. At present, NIH's total on-board strength is 21, with the following break-down by Institute:

National Institutes of Health
Senior Biomedical Research Service Appointments

NHLBI	1
NCI	5
NICHHD	2
NIDDK	6
NIDR	1
NIMH	2
NINDS	1
NLM	1
NCHGR	1
DCRT	1

DETAIL OF FULL TIME EMPLOYEES

Mr. Porter: Provide a table identifying the distribution of full-time permanent staff by grade level throughout NIH.

Dr. Varmus: The following table identifies the distribution of full-time permanent staff by grade level throughout NIH.

National Institutes of Health
Detail of End-of-Year Employment

	<u>FY 1995</u>
Executive Level IV	1
Senior Executive Service	208
GS/GM-15	904
GS/GM-14	1,307
GS/GM-13	1,339
GS-12	1,626
GS-11	1,470
GS-10	440
GS-9	960
GS-8	625
GS-7	1,560
GS-6	676
GS-5	501
GS-4	598
GS-3	178
GS-2	77
GS-1	<u>28</u>
Subtotal	12,498
Commissioned Corps:	
CC-1	2
CC-2	21
CC-3	86
CC-4	207
CC-5	223
CC-6	350
CC-7	5
CC-8	<u>7</u>
Subtotal	901
Wage Grade (all levels)	909
Ungraded	1,381
TOTAL	15,689

FUNDING FOR INSTRUMENTATION AND EQUIPMENT

Mr. Porter: How much funding for instrumentation and equipment is provided through direct costs of research project grants?

Dr. Varmus: Information is only available for equipment costs. For FY 95, we estimate that \$90 million was provided for equipment under research project grants.

FINANCIAL MANAGEMENT PLAN REVISION

Mr. Porter: Last year, you indicated that a revision to the cost management plan would be available to the Committee last summer. What is the status of the revision?

Dr. Varmus: The Financial Management Plan was revisited in 1995, reaffirming the broad overall principals and noting yearly adjustments that might be made. The principals are clear: stability, flexibility and predictability in support is important to NIH and its extramural investigators; increased costs over the life of a grant are real costs and some must be accommodated within available funds. These concepts permit stability in funding to the extramural community and flexibility to accommodate to the actual appropriation.

In this past year we had to adjust the financial management plan when, at the beginning of FY 96 NIH was working with a continuing resolution (CR) that was below the FY 95 level. NIH alerted grantees to the possibility of a suspension of the FMP through direct mailing to 13,000 and publication on the Home Page to ensure that they would be forewarned of the potential disruption in funding. Fortunately, following the full-year CR, which included a 5.8 percent increase, we were able to restore the adjustments to those awards that had been made early in the year. This information was also distributed via the Home Page (www.nih.gov) as part of our increased use of electronic communication strategies. While the increases were never specifically, mathematically tied to the BRDPI, we have attempted to adjust funding strategies to the changing costs of doing research and we expect to incorporate that information into our yearly adjustments to the FMP.

SHANNON AWARDS

Mr. Porter: Identify the amount reserved for Shannon Awards by source for FY 95-96.

Dr. Varmus: In FY 1995, 113 Shannon Awards were funded jointly by \$5 million from the NIH Director's Discretionary Fund and \$5 million from participating Institutes and Centers. Each contributed 50 percent of the overall cost of an individual award of \$100,000 for up to two years. FY 1996 funding decisions relative to Shannon Awards have not been made as yet. Traditionally, NIH formulates its Shannon funding policy late in the fiscal year in order to accumulate data on all grants

eligible after ICD funding decisions are made following the final round of grant reviews in May.

TAPS AND ASSESSMENTS

Mr. Porter: Identify the one percent set aside tap by Institute for FY96 and FY97. Also identify the other taps applied to NIH by the Department for the same time period.

Dr. Varmus: The first table displays the statutorily required one percent set-aside for Program Evaluation, not including \$4,510,000 for NIH's own evaluation program in Fiscal Year 1996 and 1997. The second table shows the taps and assessments.

National Institutes of Health Program Evaluation FY 1996 and FY 1997 Estimates (dollars in thousands)

<u>ICD</u>	<u>FY 1996 Estimate</u>	<u>FY 1997 Estimate</u>
NCI	\$16,731	\$17,482
NHLBI	10,078	10,529
NIDR	1,362	1,423
NIDDK	5,733	5,989
NINDS	5,066	5,293
NIAID	8,694	9,083
NIGMS	7,038	7,354
NICHD	4,424	4,622
NEI	2,336	2,440
NIEHS	2,147	2,243
NIA	3,374	3,525
NIAMS	1,797	1,878
NIDCD	1,312	1,371
NIMH	4,916	5,136
NIDA	3,408	3,560
NIAAA	1,476	1,542
NINR	416	434
NCRR	2,902	3,031
NCHGR	1,264	1,321
FIC	188	197
NLM	<u>1,051</u>	<u>1,099</u>
Total	\$85,713	\$89,552

National Institutes of Health
Taps and Assessments
FY 1996 and FY 1997 Estimates
(dollars in thousands)

	<u>FY 1996</u> <u>Estimate</u>	<u>FY 1997</u> <u>Estimate</u>
Program Evaluation:		
Agency for Health Care Policy & Research	\$ 44,548	\$ 39,449
National Center for Health Statistics Surveys	29,676	38,776
Assistant Secretary for Planning and Evaluation	<u>11,489</u>	<u>11,327</u>
Subtotal, Program Evaluation	\$ 85,713	\$ 89,552
National Research Service Awards:		
Primary Care (HRSA)	3,954	4,050
AHCPR (OASH)	3,954	4,050
Office of Public Health and Science Special Projects	2,855	2,777
Program Support Center	<u>15,286</u>	<u>15,622</u>
Total Taps and Assessments	\$111,762	\$116,051

GRANTS LENGTH OF SUPPORT

Mr. Porter: What share of grants are supported for the following periods, including all competitive renewals: percentage of all grants supported for five years or less; six to ten years; eleven to fifteen years; sixteen to twenty years; and more than twenty years.

Dr. Varmus: In FY 95, 15,798 awards were made for new applications or competing renewals. For 61 percent of these awards the support was for 1-5 years. Since some of these researchers may later apply for continuation of support, we cannot say what their ultimate period of support will be. For the remaining awards 19 percent were in years 6-10 of support; 10 percent were in years 11-15 of support; 6 percent were in years 16-20 of support and 5 percent were in year 21 or greater of support.

TEN YEAR HISTORY OF RESEARCH PROJECT GRANTS

Mr. Porter: Provide a ten-year table identifying the number of research project grant applications received.

Dr. Varmus: The attached table displays in total, competing research project grant applications for FY 1988 - FY 1997.

National Institutes of Health
FY 1988 - FY 1997

<u>Fiscal Year</u>	<u>Number of Applications</u>
FY 1988 Actual	21,889
FY 1989 Actual	22,021
FY 1990 Actual	22,875
FY 1991 Actual	22,197
FY 1992 Actual	22,832
FY 1993 Actual	25,140
FY 1994 Comparable	25,002
FY 1994 Realigned	25,508
FY 1995 Bud. Auth.	25,225
FY 1996 Estimate	27,469
FY 1997 Estimate	29,124

Note: For 1994 two figures are displayed to provide comparability. The first figure is comparable to FY 1988- FY 1993. The second figure reflects the realignment of research project grants which occurred in FY 1994. The realignment shifted Small Grants (RO3) and Development Grants (R21) from Other Research to Research Project Grants (RPGs), and developed a subset for the Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs to enhance logical groupings of mechanisms and accuracy of the NIH budget display.

REDUCTION OF RESEARCH MANAGEMENT AND SUPPORT

Mr. Porter: Consistent with the directive to reduce research management and support costs by 7.5 percent below FY 1995 levels, have you reduced the management and services and supply funds by a comparable amount in FY 1996? If not, why have you not reduced the tap on Institutes for these funds, since they support administrative costs that are shared by all the Institutes?

Dr. Varmus: Plans are underway to reduce the Management Fund and Service and Supply Fund supported operations to a level below FY 1995. The reduction is currently estimated to be around 3 percent. This reduction is not applied to the Clinical Research Center or the Division of Research Grants because of their unique missions and importance to ICD missions.

MULTIYEAR FUNDING

Mr. Porter: If the Committee gave you authority to use one fiscal year's appropriations to provide multiyear funding for individual grants as a way to control out year costs, would you use it?

Dr. Varmus: The NIH would prefer to use multiyear funding on a selective basis. At present we are making multiyear awards in cases where the project is small and the entire project can be managed as a single award; for example, the Shannon program. Multiyear funding authority for these programs appropriately affords scientists a flexibility consistent with their needs while eliminating an administrative burden which would be excessive for these small and short-term projects. Also, multiyear authority is valuable when a cohort of projects needs to be brought into alignment, so that they may all compete together. This may result in a 15 or 16 month award, and is done for portfolio management purposes. Widespread use of multiyear funding could limit the ability to increase or decrease levels of funding for specific programs, and could conceivably have an adverse impact on our stewardship role in monitoring spending on individual grants. Unforeseen early terminations occurring after the year of obligation would mean that recovered balances could not be applied to new research projects, and fluctuations in the annual appropriations cycles could lead to inequities in grant cohorts, i.e., researchers receiving multiyear awards in one fiscal year could receive higher levels of funding; researchers receiving funds in the next fiscal year when monies are not as plentiful could receive lower levels of support.

CLINICAL TRIALS

Mr. Porter: What should be NIH's role in funding clinical trials?

Dr. Varmus: The NIH plays an essential role in supporting clinical trials, while at the same time it actively seeks partnership with industry to develop a knowledge base that is widely accessible to the general public. The critical scientific questions posed in NIH-supported clinical trials offer little or no financial incentives for industry, but are nonetheless important for public health. The designs of many of these clinical trials carry inherent disincentives for industry sponsorship. Some examples include:

- (1) a market not big enough to justify industry investment; (2) comparisons between competing or potentially competing FDA approved drugs, biologics, or devices; (3) clinical trials of surgical procedures or clinical trials comparing surgical or behavioral interventions; (4) off-labeled use of drugs approved by FDA, but which have not been proven clinically effective; and (5) clinical trials involving drugs whose patents have expired.

The NIH supports clinical trials that evaluate pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Examples include clinical trials that evaluate vitamins or

nutritional supplements, multi-drug therapy from different manufacturers, and behavioral or life-style intervention.

In general, industry supports Phase I and Phase II clinical trials that develop data required for licensing of the drug or device by FDA. This represents an investment by the firm and the incentive is proprietary right to sale of the approved product. NIH may become involved in early testing when basic research conducted or supported by NIH identifies a potentially useful agent, device or procedure. NIH generally supports comparisons of licensed drugs or devices, evaluations of no proprietary interventions, such as diet or behavior, and often longer term evaluation of clinical outcomes (not required for licensure). Most industry-supported studies focus on changing symptoms or altering intermediates in the disease process while NIH studies are more often directed to clinical outcomes (disease development, survival, etc.). These latter studies (Phase III trials) usually provide a definitive statement about the best preventive or therapeutic approach and permit a public health recommendation regarding the best treatment. Industry may provide agents for NIH-supported trials, but cannot plan the studies or have insider knowledge of their progress.

Mr. Porter: Industry spends hundreds of millions of dollars a year on clinical trials, and NIH supports about \$1.2 billion worth. What are the guidelines for determining when a clinical trial should be funded by NIH rather than pharmaceutical companies?

Dr. Varmus: While the industry spends hundreds of millions of dollars a year on clinical trials, there are types of trials that offer no incentives for companies (as noted above). These include: (1) trials of drugs for which the market is not big enough to justify industry investment; (2) comparisons of competing or potentially competing FDA approved drugs, biologics, or devices; (3) clinical trials of surgical procedures or clinical trials comparing surgical interventions; (4) off-labeled use of drugs approved by FDA, but which have not been proven clinically effective; and (5) clinical trials involving drugs whose patents have expired.

The Institutes and Centers (ICs) of the NIH have in place specific guidelines for investigators-initiated clinical trials that describes policies and procedures for submission of such trials. In conjunction with their Advisory Council or Board, the ICs develop long-term plans that project the relevant areas of emphasis, and identify priority clinical trials that are crucial to the ICs' mission. The funding decision by the ICs depends on several factors, e.g., results of peer review, ICs Advisory Council or Board advice, importance and uniqueness of the scientific question and its impact on public health and standard of practice, costs, and the impact on future resources.

INDUSTRY SUPPORT OF BIOMEDICAL RESEARCH

Mr. Porter: In a February article in the New England Journal of Medicine, Dr. David Blumenthal did an industry survey and found that in the ten years from 1984 to 1994, life science firms were "significantly more likely to support academic research"

and they were not motivated in the main by the opportunity for short-term commercial returns. How do you envision the sharing of the cost of supporting biomedical research between NIH and industry in the next decade?

Dr. Varmus: Industry's share of total national funding for medical research has increased from 39 percent in 1984 to 52 percent in 1994, and we welcome continued growth in industry support. However, as Dr. Blumenthal's recent article confirms, most industry funding supports applied research and development. In the future, as in the past, such applied research will draw on the results of Federally funded basic research. Statistics compiled by the National Science Foundation indicate that the "drugs and medicines" industry spent less than 14 percent of its total R&D budget on basic research in 1992, while NIH spent over 60 percent of its 1992 appropriation for basic biomedical research.

Basic medical research, supported largely by the Federal government, provides the knowledge base for the growth and international competitiveness of the U.S. pharmaceutical and biotechnology industries. The private sector recognizes how vital this Federal role is. For example, in a meeting with Congressional leaders, one biotechnology executive described NIH funding of basic research as "the seed money from which America's worldwide leadership in biotechnology has sprung."

One area in which we are exploring possibilities for greater private sector involvement is clinical research. Clinical research, conducted at academic medical centers, plays a critical role in moving research findings from the laboratory bench to the patient's bedside. Researchers at these centers have traditionally relied on a mix of public and private funding, including funds generated from their own clinical practice plans. However, the spread of managed care organizations and related competitive market pressures are reducing the clinical practice revenues of academic medical centers and their ability to support research with internal funds. NIH is examining a number of steps to strengthen the prospects of clinical research including alternative financing mechanisms.

INDUSTRY IMPOSED CONSTRAINTS ON INFORMATION SHARING

Mr. Porter: Also in the article, Dr. Blumenthal noted concerns that industry imposed constraints on information sharing in the research it supported and this posed a threat to science. How serious a problem do you think this is?

Dr. Varmus: Information sharing is critical to the advancement of scientific knowledge. The NIH, academic institutions, and not-for-profit private research institutions are committed to the open exchange of data and information, and the NIH requires findings from NIH-supported studies to be shared and disseminated. We recognize that intellectual property protection may be required for the commercialization of innovations and that this may necessitate time-limited constraints on the free flow of information to allow for the filing of patent applications.

NIH strives to balance our commitment to the free flow of scientific information with the need for intellectual property protection. This issue, long discussed by scientists and research administrators, has been addressed by university and research institutions by insisting on limits on the period of publication to which they will agree. Delays which the scientific community finds acceptable seldom exceed 30-60 days. After a reasonable delay, universities and the NIH will not stop publication except by mutual agreement and under extenuating circumstances. Many companies have established streamlined processes for review of potential intellectual property arising from collaborations with academic researchers to help minimize publication delay.

QUESTIONS SUBMITTED BY CONGRESSMAN BONILLA**FUNDING FOR DIAGNOSTIC RADIOLOGY**

Mr. Bonilla: Dr. Varmus, please provide the Committee with a breakdown by Institute of intramural and extramural funding for the diagnostic radiology for Fiscal Year 1993 through 1997.

Dr. Varmus: The attached table displays the intramural and extramural funding levels for diagnostic radiology for FY 1993 - 1997 by Institute.

IMAGING EQUIPMENT

Mr. Bonilla: Please provide the Committee with a breakdown by Institute of imaging equipment used for research along with statistics on the level of utilization of each unit.

Dr. Varmus: Most of the medical imaging equipment in the NIH intramural research program is located in the Clinical Center, but some of the institutes have major imaging equipment as detailed below:

CLINICAL CENTER

Position Emission Tomography (PET): One Scanditronix PET Scanner (1983)--80 percent use

One Scanditronix PET Scanner (1988)--Full-time use plus evenings and weekends.

One GE PET Advance Scanner (1993)--Full-time use plus evenings and weekends.

Diagnostic Radiology Department:

One Magnetic Resonance Imaging (MRI) Picker 0.5T--8,626 procedures in 1995.

One Computed Tomography (CT)--GE 1.5T Signa/GE Hi-Speed (3 units) 12,486 procedures in 1995.

Ultrasound - Imatron Electron Beam CT, Acuson 128 (2 units), Diasonics Spectra VST, ATL 3000, Diasonics IVUS, Quantum--4,187 procedures in 1995.

Angiography--Angiostar, Siemens Angioscope--5,413 procedures in 1995.

General Radiology--GE MPX-80, Philips Biplane fluoro, CGR

Septar/Exatome, Siemens Thoramat Chest (2 units), GE Portable AMX-4 (4 units), Siemens Fluoro, Siemens Mammomat 2, Siemens Multix UH (2 units), --28,037 procedures in 1995.

Nuclear Medicine Department: (Total equipment listed below was estimated at 4,433 procedures for 1995).

Siemens-Orbitor single Head gamma camera

Siemens-Small Field of View (SFOV) gamma camera

Trionix TRIAD triple-headed Single Photon Emission--Computed Tomography (SPECT) gamma camera

Trionix BIAD dual-headed whole body and SPECT camera

Trionix-XLT jumbo triple-headed SPECT camera

ADAC-GENESYS dual-headed whole body and SPECT camera

ADAC VERTEX dual-headed whole-body, SPECT, and L-configuration SPECT camera

Hologic-QDR 2000 bone densitometry unit

In Vivo Nuclear Magnetic Resonance (NMR) Center (a shared facility):

Two 1.5 Tesla GE Signa MRI machines and one 4.0 Tesla Signa GE MRI machine. All are in full-time use (8 AM to 6 PM) with additional use during evenings and on weekends.

NATIONAL HEART, LUNG, BLOOD INSTITUTE

Six ECHO scanners for research purposes, as well as fully equipped catheterization and electrophysiology laboratories, both containing fluoroscopy units. All units are used regularly.

NATIONAL INSTITUTE OF DRUG ABUSE

A recently purchased Siemens HR PET scanner is being installed. An older PET tomograph is in use one day/week.

NATIONAL INSTITUTE ON AGING

Estimates of usage are as follows:

Neuroimager	800 hours per year
Phosphoimager	800 hours per year
DEXA Bone Scanner	800 hours per year
Ultrasound	1664 hours per year
NMR (30cm 1.9T)	2080 hours per year
400 MHZ Spec.	2080 hours per year

NATIONAL CANCER INSTITUTE

CT scanner (Clinac 2300 C/D (including imaging unit) in the Radiation Oncology Branch which is used 610 hours a month.

NATIONAL INSTITUTE OF MENTAL HEALTH

One SPECT - located at the Neuroscience Center/Neuropsychiatric Research Hospital at St. Elizabeth's Hospital. Usage includes 80 research scans completed on humans and 17 on non-human primates in 1995. Scan is used approximately 60 hours per week both for scans and data analysis.

NATIONAL INSTITUTE OF ALCOHOL ABUSE & ALCOHOLISM

MRI--Sigma MRI Scanner (GE 1.5 Tessler) used 3 hours per week.
PET--PC 2048-15B Scanditronics. 55 procedures 1995.

IMAGING RESEARCH PRIORITIES

Mr. Bonilla: Last year the Senate Appropriations Committee directed NIH to submit a report prior to this year's hearings describing the actions it plans to take in response, to the recommendation of the 1994 NIH conference on priorities for imaging research. Please provide the Committee with a copy of this NIH report.

Dr. Varmus: A copy of the "NIH Report on the Radiologic Conference", which was sent to the Committees on May 2, 1996, follows:

INTRODUCTION

In its report accompanying the Fiscal Year 1996 Appropriations Bill, the Senate Appropriations Committee stated the following: "At the Committee's direction, NIH recently completed a conference which found that the results of radiological science have become keystones to patient diagnosis, management, and therapy. Furthermore, as scientists push back the frontiers of understanding disease, the conferees concluded, radiological research may soon become essential for transferring many of the fundamental discoveries of molecular medicine to routine clinical practice. Given the potential radiological research holds for saving lives and lowering health care costs, the Committee directs that the NIH prepare and submit a report prior to next year's hearings describing what actions it plans to take in response to the findings of its conference on radiological research. The Committee further is supportive of the NIH maintaining the central focus afforded by the Laboratory for Diagnostic Radiology Research in the Office of the Director" (page 112). The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

BACKGROUND

The conference entitled "Developing Long Term Plan for Imaging Research" designed an extensive and comprehensive research agenda. Perhaps the single most important conclusion to emerge from the conference was the depth of important research activities across a wide spectrum of imaging issues. However, a number of research priorities appear to be particularly compelling:

Goal #1. The need to improve assessment of emerging technologies and methods in order to ensure that they are employed effectively in clinical practice. Specifically, attention should be placed on research aimed at development and implementation of high quality technology assessment in radiology.

Goal #2. The development of contrast agents and radiopharmaceuticals for improved diagnostic accuracy and effectiveness of existing technologies and methodologies:

i. The greatest priorities should be placed on the technologies that are most commonly used in radiologic practice (e.g. Computed Tomography, or CT, and

ultrasound), as well as physiologic and biochemical imaging probes (e.g. receptor- and cell-directed SPECT, PET and MR agents; markers of hypoxia; energy utilization tracers).

ii. Expanding the methods to take advantage of advances in molecular biology has the utmost priority. For example, development of specific cellular, genetic and receptor-targeting imaging agents.

Goal #3. Further development and utilization of magnetic resonance imaging (MRI) and spectroscopy (MRS) in clinical practice and basic research. Specifically, development of advanced MRI technologies and methodologies, such as high speed imaging, design of quantitative methods for assessing physiologic parameters (e.g. perfusion and flow) and application of MRI methods to metabolic tissue characterization.

Goal #4. Integration of imaging techniques (such as MRI, CT and ultrasound) with minimally invasive tissue diagnosis (e.g. biopsy) and treatment administration (e.g. lasers, focused ultrasound, and cryosurgery) should have the highest priority.

Goal #5. Design and evaluation of cost-effective technologies and methodologies for disease screening and prevention, including but not limited to oncologic (e.g. breast, gastrointestinal, prostatic and ovarian cancer) and cardiovascular diseases.

Goal #6. Development, evaluation and implementation of digital image acquisition in order to improve image quality compared to film-based technologies. In addition, digital technologies would allow for electronic image processing and analysis for enhanced image interpretation, and transmission, or teleradiology, for facilitated expert consultation.

ACCOMPLISHMENTS

1) High Quality Technology Assessment Studies (Conference Goal #1). The Radiologic Diagnostic Oncology Group (RDOG) was formed by the NIH in response to an RFA. The RDOG objective is timely evaluation of current and emerging imaging modalities in the management of patients with cancer. The development of multi-institutional clinical trial groups allows for rapid patient accrual within a short period of time. This, in turn, ensures rapid evaluation and optimization of imaging techniques for diagnosis, staging, and serial monitoring of cancer. The RDOG has had a significant impact on clinical research in radiology. This is the first time that multi-institutional clinical trials in diagnostic imaging have been conducted in a centrally coordinated fashion with strict quality control and analysis of cost-effectiveness. Ultimately, it is hoped that the RDOG study findings would be useful for design of therapeutic protocols and formulating clinical strategies and medical insurance reimbursement policy. Since the time of its establishment, RDOG clinical research has been important for the development of optimal imaging algorithms for prostate and lung cancer (RDOG I), pancreatic and colon cancer (RDOG II). More recent

studies in musculoskeletal and head and neck tumors (RDOG III), ovarian and pediatric solid tumors (RDOG IV) and image-guided stereotactic breast needle biopsy as a minimally invasive, cost-effective alternative to surgical diagnosis (RDOG V) are currently in final stages of patient accrual and statistical analysis. The projected budget for the successful continuation of high quality technology assessment programs to achieve the goals defined by the conference is about \$3 million per year.

2) Integration of Tumor Diagnosis and Treatment (Conference Goal #4). Over the last several years, image-guided tumor diagnosis and therapy (IGDT) emerged as a revolutionary direction in medicine and surgery, with a potential to replace some of the major surgical procedures with ambulatory, minimally invasive radiologic, computerized percutaneous interventions. Jointly with NASA, Ballistic Missiles Defense Organization (formerly SDI) and the Society of Cardiovascular and Interventional Radiology (SCVIR), NIH initiated a Joint Technology Transfer Program in order to identify space, intelligence and defense technologies that may advance the current state-of-the-art in IGDT. This effort will encompass such diverse technologic areas as 3-D Imaging, intraoperative guidance, real time imaging, virtual reality, surgical workstation design, telepresence/telesurgery, telerobotics, and telecommunications. A national search for promising intelligence, space and defense technologies will be conducted in FY 1996. If promising technologies are identified, the funds required for the successful completion of this program in FY 1997 have been estimated at about \$2 million per year for a period of five years.

3) Design and Evaluation of Cost-Effective Technologies and Methodologies for Disease Screening and Prevention, including Digital Imaging (Conference Goals #5 and 6). The examples of the NIH programs in the area of breast cancer screening are provided below:

I. National Digital Mammography Development Group (NDMDG). This Interactive Program Announcement (PA) established an international multi-institutional, multidisciplinary collaboration of academic centers, industry and NCI that facilitated a comprehensive development and validation of the full-field digital mammographic systems. The preliminary data in phantoms and healthy volunteers show that digital mammography may improve image quality (e.g. by increasing lesion-to-background contrast) at lower radiation dose. In addition, preliminary results generated by the Group indicate the following: a) the importance of image processing in improvement of breast cancer diagnosis in women with radiodense breast tissue; and b) the role of computer-aided diagnosis in automated identification of clustered microcalcifications missed in a routine mammographic clinic. This program, representing the first partnership between NCI and imaging industry, serves as an important example of the role of government-industry-academia collaborations in the facilitated development of high-risk, high-impact technologies. This program is currently funded at about 30 percent of the peer review-recommended level, and enhanced support (at about \$1 million per year) will facilitate further development, evaluation and implementation of this technology in FY 1997-1998.

ii. Federal Technology Transfer Program in Digital Mammography. The goal of this program is to advance the current state-of-the-art in digital mammography through transfer of digital imaging technologies originally developed for space, military and intelligence applications. This program has been supported jointly by NCI and NASA (six major multidisciplinary consortia of investigators from radiologic, space and military communities were funded, with annual budget of about \$1.9 million). For successful continuation of this program, additional annual support of about \$1 million will be critical in FY 1997.

iii. Novel Non-Ionizing Radiation Technologies for Breast Cancer Imaging. The goal of this Program Announcement is to stimulate the development and validation of such technologies as Ultrasound, MRI/MRS, optical imaging, microwave and other relevant areas for the detection and characterization of breast cancer. This program supports a full range of studies, from basic instrumentation and technology development to their preclinical and clinical evaluation. Preliminary data supported by this program and generated by the University of Pennsylvania and Baylor University indicate that breast MRI emerged as one of the promising novel technologies for breast cancer detection in women with fully radiodense/radio-opaque breast tissue. Specifically: a) breast MRI detects lesions as small as 1-3 mm; b) accuracy of breast MRI for breast cancer detection is considerably higher compared to conventional x-ray mammography; c) technologic improvements, such as high resolution breast MRI, are expected to improve breast cancer detection and characterization even further; d) breast MRI has been shown to improve definition of local anatomic tumor extent critical for treatment planning. To support development and validation of other screening imaging technologies will require an annual budget estimated at about \$4 million.

CURRENT PLANS

Development of Technologies and Methodologies for Improved Diagnostic Accuracy and Effectiveness of Existing Technologies and Methodologies, Including Physiologic, Biochemical and Cellular Probes (Goals #2 and #3). The following programs have been formulated recently in order to accomplish these goals:

i. MRS Biochemical Markers and Tumor Cell Biology (\$1 million per year; total of five years); ii. Quantitative Tumor Receptor Imaging (\$1 million per year; total of five years); and iii. MR Contrast Agents: Quantitative Imaging of Tissue Function (\$1 million per year; total of five years). iv. MRS Biochemical Markers and Tumor Cell Biology.

MRS opens a unique, multiparametric, multinuclear, non-invasive in vivo evaluation of unperturbed tissue metabolism and biology. Current data indicate that MRS markers have been shown to play a role in prognosis, diagnosis and therapeutic response assessment of cancer. More recently, MRS emerged as the tool for studies of drug metabolism. The clinical role of MRS is currently under investigation (e.g. differentiation of normal from malignant tissue). MRS parameters may reflect phospholipid metabolism (e.g. cell membrane synthesis and catabolism), pH,

bioenergetic metabolites, tissue oxygenation and other measurements. MRS may open interesting possibilities in quantitative characterization of tumor oxygenation, cell proliferation and drug resistance, and such information is expected to be important for therapeutic planning. The overall goal of this research is to address relationship between MRS markers and such important areas in cancer cell biology as cell membrane metabolism, tumor physiology, genetic markers, cell growth receptors and drug pharmacokinetics, as well as their role in tumor diagnosis, treatment planning, and drug development.

ii. Quantitative Tumor Receptor Imaging Receptor-targeted imaging strategies in Positron Emission Tomography (PET) of cancer have the potential of not only more specifically sub-classifying cancers based on cell receptor expression, but also are promising as the means to increase the predictive accuracy of PET relative to response to specific treatment regimens. Further studies are required for synthesis and evaluation of improved agents. One of the most promising areas of this research appears to be identification, and quantitation of estrogen and progesterin receptor systems in breast cancer, as well as evaluation of their saturation (or completeness of their blockage) by the appropriate therapeutic agents.

iii. MR Contrast Agents: Quantitative Imaging of Tissue Function Contrast-enhanced functional MRI appears to be promising for measurements of physiologic tumor parameters. However, further research is required to develop, optimize and evaluate such functional MRI-based measurements as tissue perfusion, blood flow and volume, diffusion, permeability, oxygenation, interstitial space and pressure, and water exchange rates. While this research will examine the clinical utility and implications of these measurements, it is also expected to address two fundamental challenges in contrast-enhanced functional MRI: development of mathematical modeling for correlation of MR signal intensity and contrast agent concentration; and integrated development of MR instrumentation and contrast agents.

CONCLUSIONS

In summary, the Conference on Developing a Long-Term Plan for Imaging Research identified and highlighted numerous emerging, promising scientific areas in radiology. Currently, the Conference recommendations, as described above, are in various stages of research support and planning. It is anticipated that improved funding of radiologic research will increase the likelihood of the successful implementation of the conference recommendations.

IMPLEMENTATION OF IMAGING CONFERENCE RECOMMENDATIONS

Mr. Bonilla: Does NIH have a plan to support the research recommended by the Conference?

Dr. Varmus: Several programs were established to implement the recommendations of the Conference. As detailed in the report, these include support for Magnetic Resonance Spectroscopy (MRS) for use in detecting biochemical

markers and in the study of tumor cell biology, Quantitative Tumor Receptor Imaging, and the development of new MR contrast agents for Quantitative Imaging of Tissue Function. Implementation of these programs is in various stages.

RECOMMENDATION FOR IMAGING RESEARCH

Mr. Bonilla: What changes in the organization of imaging research at NIH are needed to undertake this research efficiently and effectively?

Dr. Varmus: A detailed analysis of organizational changes needed in the intramural research program at the NIH is included in the report of an intramural Imaging Task Force. No organizational changes are currently recommended for extramural imaging support.

LABORATORY OF DIAGNOSTIC RADIOLOGY RESEARCH

Mr. Bonilla: Several years ago NIH established the Laboratory of Diagnostic Radiology Research (LDRR) in response to direction from Congress, has LDRR realized its potential as a center for imaging research?

Dr. Varmus: LDRR is one of several independent imaging laboratories in various institutes on the NIH campus. LDRR is not the center for imaging research at the NIH and at this time there are no plans to centralize imaging research under one program or laboratory on the NIH campus. LDRR's major function is to provide training for radiologists and nuclear medicine physicians in basic and clinical research not available at other academic institutions so that these individuals will be fully trained in state-of-the-art diagnostic radiology research. The laboratory provides customized training for each of the fellows in the program including opportunities to take training courses in addition to carrying out their own individual research projects under the supervision of a mentor selected from the scientists at NIH. In November 1994, LDRR underwent its first extramural scientific review which praised the science it has been able to accomplish and suggested that LDRR would be able to achieve its training and research goals with more slots for fellows and an environment more conducive to interactions with other imaging centers at the NIH than its current organizational and physical location in the Office of the Director. The LDRR will move to the Clinical Center.

LDRR's Multimodality Radiological Image Processing Section (MRIPS) which is run without FTEs and funded through the Management Fund at the NIH, does provide a central image processing facility including image processing programs, high speed networking and approximately one terabyte of disk space for each imaging scientist to store their research. Presently all Computerized Tomography and Magnetic Resonance Imaging examinations performed in the Clinical Center are sent automatically to the MRIPS disk space which is available to researcher and clinicians within 30 minutes after the studies are completed.

PLANS FOR LABORATORY OF DIAGNOSTIC RADIOLOGY RESEARCH

Mr. Bonilla: What are your future plans for Laboratory of Diagnostic Radiology Research (LDRR)?

Dr. Varmus: Following the analysis of a Task Force on Imaging Research at the NIH and confirmation by outside review of the need for additional resources and interactions with other imaging scientists, a Memorandum of Understanding was established between the Office of Intramural Research and the Clinical Center. By this agreement, LDRR is to be relocated into the Clinical Center once an appropriate new Director is recruited and on board in the Diagnostic Radiology Department, Clinical Center. LDRR will be the research imaging laboratory for the Diagnostic Radiology Department. With the relocation of LDRR into the Clinical Center, it can be provided with additional FTE's (including a mechanism to recruit fellows) and resources will be sought to create an experimental physiology laboratory which will include: experimental angiography, spiral computerized tomography, MR microscopy, ultrasound, and single photon emission tomography imaging capabilities for the program.

Mr. Bonilla: What resources will LDRR need in the coming years?

Dr. Varmus: The FY 1997 President's budget provides \$1.9 million and nine full-time equivalents (FTEs) to support the LDRR. In addition, LDRR's Multimodality Radiological Image Processing Section (MRIPS), which is run without FTEs, is funded at a level of \$635 thousand through the NIH Management Fund. Decisions on resource requirements for future years will be made after a new Director of Diagnostic Radiology has been appointed.

Mr. Bonilla: Does NIH have plans to provide those resources?

Dr. Varmus: Currently, NIH plans to relocate the LDRR in the Clinical Center, probably in FY 1997. When a new Director of Diagnostic Radiology has been appointed, a decision will be made on the number of new FTEs, office and laboratory space and the new level of funding required.

LABORATORY OF DIAGNOSTIC RADIOLOGY RESEARCH FELLOWS

Mr. Bonilla: Last year you indicated that LDRR had only about one-half of the planned number of training fellows because of FTE issues related to the location of the Lab in the Director's office. Have the FTE problems been solved?

Dr. Varmus: The relocation of LDRR to the Clinical Center should create an appropriate environment for a solution to this problem.

IMPROVEMENT OF IMAGING RESEARCH AT NIH

Mr. Bonilla: What plans exist for the general improvement of imaging research at NIH?

Dr. Varmus: An extensive analysis of this question was undertaken by a Task Force of Imaging Research at the NIH and several suggestions were made for improvements including better coordination of imaging research by creation of an Imaging Working Group, recruitment of a new chair of the Department of Diagnostic Radiology in the Clinical Center who would also serve as Associate Director for Imaging in the Clinical Center and development of a more formal training program for fellows in imaging research. In addition, the Director of the Clinical Center and the Deputy Director for Intramural Research have signed a Memorandum of Understanding which will transfer the Laboratory of Diagnostic Radiology Research (LDRR) to the Department of Diagnostic Radiology where it will become the research arm of this department.

IMAGING TASK FORCE

Mr. Bonilla: Last year you indicated that the Deputy Director for Intramural Research and the Associate Director for Clinical Research had organized an Imaging Task Force in response to recommendations of a meeting of extramural imaging scientists and a work group of intramural imaging experts convened in early 1995. Please provide the Committee with the final report of the extramural scientists and intramural working group.

Dr. Varmus: The final "Report and Recommendations of the NIH Imaging Task Force," dated August 9, 1995, is attached for your information.

COORDINATION OF IMAGING ACTIVITIES

Mr. Bonilla: What specific measures has the Imaging Task Force recommended to improve the coordination of imaging activities throughout NIH?

Dr. Varmus: Several specific measures to improve coordination of imaging activities at the NIH are proposed in the report of the Imaging Task Force, including: (1) Reconstitution of the Task Force as an "Imaging Working Group" to discuss issues of general concern including the need for new resources, sharing of resources, and new directions for imaging research at the NIH; (2) There should be a regular meetings, including outside consultants, to evaluate the progress of coordination of imaging activities at the NIH; (3) A training program involving both basic science and clinical researchers should be created at the NIH; (4) A new Chair of the Department of Diagnostic Radiology in the Clinical Center should be recruited to serve as a leader of imaging on the NIH campus. This person should also be the Associate Director for Imaging in the Clinical Center.

NEW DIRECTOR FOR DEPARTMENT OF DIAGNOSTIC RADIOLOGY

Mr. Bonilla: How will recruitment of a new director for the Department of Diagnostic Radiology promote collaboration among the various departments at NIH?

Dr. Varmus: It is anticipated that the new Chief of the Department of Diagnostic Radiology in the Clinical Center will be an energetic, forward thinking, and dynamic individual who will become the natural leader of imaging activities at the NIH. To foster this role, the Chief of Diagnostic Radiology will also be the Associate Director for Imaging in the Clinical Center and will be a key individual on the "Imaging Working Group" which was established by recommendation of the "Report of the Imaging Task Force." The Laboratory of Diagnostic Radiology Research, by mutual agreement between the Deputy Director for Intramural Research and the Director, Clinical Center, will become the research arm of the Department of Diagnostic Radiology, thereby joining an important clinical program with a critical diagnostic radiology research and training program.

QUESTIONS SUBMITTED BY CONGRESSMAN ISTOOK

HUMAN EMBRYO RESEARCH

Shortly after Congress passed a prohibition on federal funding for the creation of human embryos for research purposes or destructive research on human embryos through FY 1996, Congressional Quarterly's Congressional Monitor reported that "the Clinton administration said [the prohibition] 'limits' such research and would have no effect on federal projects."

Mr. Istook: What is the status of NIH, or NIH-supported, research on human embryos?

Dr. Varnus: The NIH has not funded any human embryo research. During 1994 and 1995, NIH was engaged in a process to develop policy and ethical guidelines for the funding, review, and conduct of such research. Section 128 of P.L. 104-99 enacted in January 1996, states that "None of the funds made available by Public Law 104-91 may be used for--(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and 42 U.S.C. 289g(b). For purposes of this section, the phrase 'human embryo or embryos' shall include any organism, not protected as a human subject under 45 CFR 46 as of the date of enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes." Further background information is provided below about NIH's effort in regard to this area of research.

"Human embryo research" should actually be termed "human in vitro fertilization (IVF) and preimplantation embryo research" or, more simply, "human IVF research." This research involves the fertilization of a human egg in a petri dish and the earliest cell divisions of the resulting fertilized egg or preimplantation embryo. It is important also to explain what the term "preimplantation" means. As it occurs under normal circumstances in the body, implantation is the point at which the fertilized human egg begins to implant into the wall of the uterus, a process that starts at about the seventh day of development and is completed about the fourteenth day of development. At this stage of development, the preimplantation embryo, consisting of a few dividing, undifferentiated cells, is about 0.5 mm in diameter, smaller than the period at the end of this sentence.

The technology of human in vitro fertilization has been available since 1978, but research in this area has never been funded by the Federal government. Between 1980 and 1993, Federal regulations required that human IVF research be reviewed by a national ethics advisory board in addition to the local level ethical review that occurs for all studies involving human subjects. Since the board did not exist during that period of time, no proposals could be considered for funding. In 1993, Congress nullified this requirement in P.L. 103-43, making it possible for NIH to consider funding this research.

Mr. Istook: How many projects involving research on human embryos, in utero or ex utero, and including IVF research, have been funded and at what cost?

Dr. Varmus: The NIH has not funded any human embryo research. During 1994, the NIH carefully and openly considered the policy issues surrounding Federal funding of research involving human IVF and the preimplantation embryo. NIH organized a multi-disciplinary panel of experts--composed of 19 people from outside government with diverse background in science, ethics, law, sociology, theology, public health, and public policy--to study the ethical, scientific, medical, and public policy implications of Federal funding of this research. The work of this panel was carried out in open forums, involved substantial public input, and led to the formulation of recommendations for stringent guidelines that would govern the review and conduct of any future research that might be considered for funding by the NIH.

The panel learned about the potential of human IVF research to improve human health. In addition to advancing research aimed at treating infertility, the panel found that such research could result in knowledge about preventing birth defects and understanding the activity of oncogenes that play a role in causing cancer. They also found that research on embryonic cells could lead to a source of universally compatible cells for transplantation. These cells hold enormous potential to treat a wide range of diseases such as leukemia, sickle cell anemia, Parkinson's disease, and spinal cord injury.

After considering these potential benefits, ethical and moral issues, and the range of public sentiments, the panel concluded that certain areas of research involving human IVF and the preimplantation embryo should be acceptable for federal funding within a framework of stringent federal guidelines. The panel provided detailed recommendations about what those guidelines should include. The panel further concluded that in certain very limited circumstances, it was also acceptable to fertilize human eggs expressly for research purposes. This is sometimes referred to as "the creation of human embryos for research purposes."

On December 2, 1994, the Advisory Committee to the Director, NIH (ACD) reviewed and approved the panel's recommendations, including the recommendation that a special review committee be established to monitor ethical and scientific issues associated with the research on a continuing basis and to review all research proposals in this area before any funding was permitted. The ACD also strongly affirmed another recommendation of the panel that NIH should continue its efforts to enhance public understanding of the nature of this research. On December 2, 1994, the President issued a directive that NIH not allocate any resources for research involving "the creation of embryos for research purposes".

HUMAN EMBRYO RESEARCH PANEL RECOMMENDATIONS

Mr. Istook: What steps, if any, has NIH taken on the recommendations of the human embryo research advisory panel that issued its report last year?

Dr. Varmus: On December 2, 1994, the President issued a directive that NIH not allocate any resources for research involving "the creation of embryos for research purposes". The NIH has not funded any human embryo research. The President's directive meant that the NIH could not fund research involving in vitro fertilization of a human egg for research purposes. The directive did not affect research involving embryos that result from the clinical treatment of infertility or other medical problems. With appropriate and specific consent from both parents, along with required ethical and scientific review of proposals, such embryos could be studied to gain important knowledge for the benefit of human health.

During 1995, the NIH began to develop plans to establish the advisory committee recommended by the panel and the ACD for the review of those proposals that would have been permitted under the President's directive. Along with a central function to enhance public understanding about research involving human IVF and the preimplantation embryo, the committee would also monitor ethical and scientific issues associated with this research on a continuing basis. One of the committee's first tasks would also be to finalize guidelines to govern the review and conduct of research, guidelines based on the panel's recommendations.

HUMAN EMBRYO RESEARCH FUNDING PROHIBITION

Mr. Istook: What is your understanding of the human embryo research funding prohibition in P.L. 104-99?

Dr. Varmus: In January 1996, an amendment was included in P.L. 104-99 prohibiting funding of research involving human IVF and the preimplantation embryo. The amendment applies to both research that was restricted by the President -- "the creation of human embryos for research purposes" -- as well as research that would have been allowed under his policy, i.e., research with preimplantation embryos resulting from clinical treatment for infertility as well as research on parthenogenesis. Parthenogenesis involves studies with human eggs that begin dividing through artificial activations, not through fertilization with sperm, and stop at a very early point with no potential to become an embryo.

No ongoing research was affected by the amendment because none has been funded.

MIFEPRISTONE RESEARCH

On January 11, 1994, the Federal Register carried a notice that the National Advisory Child Health and Human Development Council meeting would include in its agenda "a report by the Director, NICHD of the IOM report on Clinical Applications of Mifepristone RU 486 and Other Antiprogestins..."

Mr. Istook: What types of research on RU 486 are or have been conducted or supported by NIH?

Dr. Varmus: Mifepristone, or RU 486, is an antiprogesterin drug that blocks the effects of two steroids in the body, progesterone and glucocorticoid. It is now being studied as a possible treatment for certain diseases that are believed to be influenced by progesterone such as a type of brain tumor, breast cancer, and endometriosis. It is being used in reproductive biology and physiology studies aimed at understanding the processes involved in human fertility and infertility. It also serves as an important tool for advancing laboratory research studies. The NIH has never funded studies of RU 486 as an abortifacient.

One of the most important NIH efforts underway with RU 486 involves a clinical study of its efficacy in the treatment of the brain tumor called meningioma. A new approach to the treatment of this type of brain tumor is greatly needed because surgery and radiation sometimes cannot be employed, and there are currently no therapeutic agents that can retard its growth. RU 486 was initially tested in meningiomas because these tumors frequently carry progesterone receptors. This tumor is considerably more common in women and especially women with a history of breast cancer.

RU 486 is also being used, along with other inhibiting or stimulating factors, in studies aimed at characterizing normal and abnormal reproductive processes. Some of this research focuses on regulation of ovulation and the menstrual cycle in animals. Other research is investigating the etiology and pathophysiology of disorders such as amenorrhea, chronic anovulation, endometriosis, luteal phase defects, and premenstrual syndrome. RU 486 is also being used to study possible causes of preterm labor and the management of labor. RU 486 is being studied in animals as a possible hormonal contraceptive agent. Other studies are investigating the effects of RU 486 on cervical mucous and on the formation of ovarian follicles, research that may lead to further developments in the area of fertility regulation.

Other basic studies involving RU 486 are advancing understanding of the regulation of tumor growth, including central nervous system tumors and uterine leiomyomas, and the body's immune responses to tissue injury and infections. RU 486 is being used in the study of the regulation, expression, structure, and degradation of steroid receptors. Many breast cancers develop resistance to the anti-steroids that are used to treat them, and some research is focused on determining how this resistance evolves. This work may ultimately lead to the development of new treatments.

Studies with RU 486 are also aimed at understanding the role of steroids in response to stress. One study on this topic, which may help in efforts to reduce the effects of stress on metabolism, is looking at the impact of glucocorticoids on thyroid function and dysfunction. Other studies in animals involve the role of steroids in adaptation to repeated stress, familial stress, drug-taking behavior, and stress resulting from surgery.

RU 486 is also being studied to understand more about the role of glucocorticoids in obesity and non-insulin dependent diabetes mellitus. This work is using RU 486 to determine the role of glucocorticoids on the development of obesity

in rats that have mutations in the *fatty* gene. A clinical study is being done to determine whether RU 486 will induce loss of appetite, increased metabolism and weight loss in obese men.

RU 486 is also being used in the development of better gene therapy strategies. New gene vectors are being developed that have a "gene switch." This switch will be regulated specifically and selectively by antiprogestins, such as RU 486. These vectors are being used to study animal models for Parkinson's disease and mucopolysaccharidoses, diseases that result from the body's inability to degrade certain sulfates, and affecting multiple organ systems, tissues and the skeletal system.

Mr. Istook: What is (or was) the cost of such research, and what is the Federal share of the costs?

Dr. Varmus: In FY 1995, NIH support for research involving RU 486 totaled \$3.6 million.

Mr. Istook: Please provide a list of the recipients of NIH funding for research using RU 486, the type of research being conducted, and the amount of Federal funds provided to each recipient.

Dr. Varmus: A list is attached of the recipients, project titles, recipient institutions, and amounts of NIH funds provided to each project in FY 1995 for research involving RU 486.

Recipients of FY 1995 NIH Funds for RU486 Research

Name of Investigator	Title of Research Project	Recipient Institution	Amount of FY95 Funds for Project
Berger, Nathan	CWRU Cancer Research	Case Western Reserve University	\$6,487
Chrousos, George B.	Endocrine-Immune Interactions	NIH Intramural	\$78,239
Collins, Sheila	Steroid Regulation of B-Adrenoreceptor Genes in Obesity	Duke University Medical Center	\$108,345
Daynes, Raymond	Efferent Control of Cellular Immune Responses	University of Utah	\$11,257
De Franco, Donald B.	Glucocorticoid Receptor Function in Hypothalamic Cells	Pittsburgh University	\$150,921
De Franco, Donald	Intracellular Mechanisms of Glucocorticoid Action	University of Pittsburgh at Pittsburgh	\$23,373
Dey, Sudhansu K.	Aspects of Blastocyst Implantation	University of Kansas Medical Center	\$36,767
Distelhorst, Clark	Development Program in Breast Cancer	Case Western Reserve University	\$5,407
Eckhart, Walter	Cancer Centers	Salk Institute for Biological Studies	\$18,420
Edwards, Dean P.	Steroid Antagonists and Resistance in Breast Cancer	Colorado University Health Sciences Center	\$156,165
Edwards, Dean	Progesterone Receptor Binding to Specific DNA Sequences	University of Colorado Health Sciences Center Denver	\$9,440
Edwards, Dean	Cancer Center Breast Cancer Research Program	University of Colorado Health Sciences Center Denver	\$0*
Gelehrter, Thomas	Hormonal Regulation of Membrane Phenotype	University of Michigan at Ann Arbor	\$20,971
Glorioso, Joseph C.	Gene Therapy of Mucopolysaccharidoses Using HSV Vectors	Pittsburgh University	\$236,545
Goeders, Nicholas E.	Environmental Influences on Cocaine Self-administration	Louisiana State University School of Medicine	\$15,853
Grunberg, Steven	Phase III Clinical Trial of RU486 for the Treatment of Meningiomas	Southwest Oncology Group-Clinical Trials (Cooperative Group Clinical Trial)	\$133,540
Haslam, Sandra	Stroma and Mammary Gland Cell Proliferation	Michigan State University	\$34,487
Horvitz, Kathryn	Progesterone Receptor in Breast Cancer	University of Colorado Health Sciences Center Denver	\$29,266
Horvitz, Kathryn	Phosphorylation of Breast Cancer Progesterone Receptors	University of Colorado Health Sciences Center Denver	\$37,645
Horvitz, Kathryn B.	Tissue Specific Effects of Progesterone	Colorado University Health Sciences Center	\$222,544
Jordan, Virgil	Structure Function Relationship of Antiestrogen	University of Wisconsin Madison	\$0*
Katzeneellenbogen, Benita	Antiestrogens—Mechanism of Antagonist Action	University of Illinois Urbana-Champaign	\$11,573
Mahesh, Vinendra B.	Effect of Progesterone on Gonadotropin Secretion	Medical College of Georgia	\$40,963
Mc Donnell, Donald P.	Genetic Dissection of Progesterone Receptor Function	Duke University Medical Center	\$204,572
Moore, Michael	Progesterin Stimulation of C-MYC and Breast Cancer Growth	Marshall University	\$0*

Name of Investigator	Title of Research Project	Recipient Institution	Amount of FY95 Funds for Project
Moudgil, Vininder K.	Interaction of Nucleotides and Steroid Receptors	Oakland University	\$132,660
Munck, Allan U.	Cell Cycle and Glucocorticoid Receptor Phosphorylation	Dartmouth Medical School	\$168,626
Myatt, Leslie	The Hormonal Regulation of Myometrial Activity	University of Cincinnati	\$151,889
Nieman, Lynette K.	Steroid Hormone Action in Female Reproduction	NIH Intramural	\$21,733
Nordeen, Steven K.	Molecular Mechanisms of Glucocorticoid Hormone Action	Colorado University Health Sciences Center	\$145,137
Novy, Miles J.	Endocrine and Vascular Relationships in Parturition	Oregon Regional Primate Research Center	\$91,103
Samuels, Mary H.	TSH Secretion—Role of Glucocorticoids	Oregon Health Sciences University	\$96,374
Samuels, Herbert H.	Metabolic Effects of Thyroid Hormone	New York University Medical Center	\$545,973
Schwartz, Neena B.	Environmental and Hormonal Interplay of Ovulation	Northwestern University	\$20,562
Stouffer, Richards L.	Contraception with Mini Dose Antiprogestin in Macaques	Oregon Regional Primate Research Center	\$360,899
Thomas, Thresia	Polyamines and Estrogen Function and Breast Cancer	University of Med/Dent NJ-RW Johnson Medical School Piscataway, NJ	\$19,662
Truett, Gary E.	Physiologic Basis of FA Gene Recessivity	Pennington Biomedical Research Center, Baton Rouge, LA	\$92,828
Unger, Roger H.	Mifeprestone Effect on Appetite and Weight Loss in Obesity and Non-Insulin Dependent Diabetes Mellitus	University of Texas Sw Medical Center Dallas, Texas	\$507
Walker, Cheryl L.	Model for Screening Anthrormonal Therapies for Leiomyoma	Ligand Pharmaceuticals	\$99,494
Weigel, Nancy	Regulation of Human Steroid Receptors by Phosphorylation	Baylor College of Medicine	\$74,765
Yen, Samuel S.	Chronic Anovulation: Mechanisms and Consequences	University of California, San Diego	\$21,976
TOTAL \$			\$3,636,988

*These projects were funded in the previous year but are still active.

POPULATION RESEARCH

On seeing a partial list of discretionary budget expenditures of HHS over a period of two and a half years, I noted that, just in the first three months of fiscal year 1995, several million dollars were given in dozens of grants under the program title "population research." Hundreds of millions of dollars in NIH grants were spent for "population research" in FY 1994, including \$338,843 to the Alan Guttmacher Institute, the research affiliate of the Planned Parenthood Federation of American (PPFA).

Mr. Istook: Please explain the types of research that are funded as "population research," as well as provide a list of the recipients of federal funds for this category of research with the amounts of federal funds they received.

Dr. Varmus: The NIH supports a broad program of population research. This program is carried out through the support of research and research training in the biomedical, demographic and behavioral sciences. Funding is provided through grants and contracts for fundamental biomedical research in the reproductive sciences relevant to the problems of human fertility and infertility; the development of safe and effective methods for fertility regulation; the evaluation of the benefits and risks of current contraceptive methods and non-contraceptive gynecological products or procedures; and demographic and behavioral sciences research on the causes and consequences of population structure and change. The major source of NIH support for population research is the National Institute of Child Health and Human Development (NICHD). However, other Institutes within the NIH also support research in this area. A list is attached of the recipients, project titles, recipient institutions, and amounts of NIH funds provided to each project in FY 1995 for population research. It is important to emphasize that none of the studies of fertilization and early embryo development involved human in vitro fertilization or human preimplantation embryos. All such studies were performed in animal models.

Mr. Istook: Also, please provide a list of the grants that the NIH has provided to the Alan Guttmacher Institute, or Planned Parenthood Federation of America, in the last five years, together with an explanation of the projects' purposes and findings.

Dr. Varmus: During the last five years, three NIH grants have been awarded through NICHD to the Alan Guttmacher Institute for the conduct of two research projects. Descriptions of the two projects awarded to the Alan Guttmacher Institute are as follows.

- "Planning Status of Births and Infant Health" -- The purpose of this project is to examine whether, and how, infant health outcomes are affected by whether a birth results from a planned pregnancy or one that is unwanted or mistimed. The project is studying the associations between the planning status of births, maternal behaviors during pregnancy and after the birth, and infant health outcomes to test hypotheses about the mechanisms through which unplanned pregnancy may affect infant outcomes and the circumstances under which such

effects are greatest. Data gathered through the project is currently being analyzed. One finding published thus far regarding the social and demographic factors associated with unplanned childbearing show that a birth is most likely to be unwanted or mistimed if the mother is unmarried, young, or poor (Kost and Forrest, "Intention Status of U.S. Births in 1988..." Family Planning Perspectives 27(1), January/February 1995). This project received \$30,000 in FY 1993, \$119,417 in FY 1994, and \$148,458 in FY 1995.

- "Contraceptive Effectiveness and Unintended Pregnancy" -- The purpose of this project is to improve knowledge about the ability of American couples to prevent unintended pregnancy through contraceptive practice. By overcoming deficiencies in existing survey data on this topic, the study will yield accurate estimates of the effectiveness of different contraceptive methods, information on trends in method use-effectiveness, and a wealth of information about the factors that contribute to effective contraceptive use. The study is still underway so no findings are yet available. This project received \$219,426 in FY 1994 and \$118,732 in FY 1995.

Mr. Istook: Additionally, please provide a list of grants NIH has provided, in the last five years, to all affiliates of Planned Parenthood Federation of America. With that list, please describe the intent and findings of the research done by affiliates of Planned Parenthood Federation of America.

Dr. Varmus: Neither Planned Parenthood Federation of America nor any of its affiliates other than the Alan Guttmacher Institute received NIH support during the last five years.

[Clerk's Note: The requested material was deemed too lengthy for printing and has been retained in Committee files.]

RESEARCH ON SPECIFIC DISEASES

Mr. Istook: I discussed the document, "Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support," dated November 1995, at the hearing. From this report it is clear that, if science were influenced by the needs of society in some fashion, through a confluence of the number of people affected, costs to society, and costs to the taxpayer, plus opportunities for research from the medical community, some general criteria for allocation of research dollars should be possible. You seem to have hinted at that in your comments to the Senate during the reauthorization hearings when you discussed terms like "chronic disabling diseases" that cross Institute lines within NIH. I would like the following information compiled: (which does not need to be submitted for the record. I recognize the extensive nature of this request.)

- i. The number of grant applications for each type of disease: (mentioned in the report table)
- ii. The amount of money requested for research for each type of disease.
- iii. The number of grants awarded and amounts of money approved for each type of disease.

Dr. Varmus: I appreciate your questions and the opportunity to explain why we do not have the information available in the exact fashion in which you have asked for it. Generally, the NIH does not compile information about which specific diseases, if any, are proposed to be researched through individually submitted grant applications. Therefore, the amount of money requested for each disease is not known. Generally, only through an after-the-fact review of actually awarded grants can estimates be derived of grant spending for particular diseases. It is from such reviews that projections of spending for specific diseases are made for budget request display purposes. Regardless, I am very cautious about attempting to link the amount of money we spend on any disease or the number of grant applications for the study of a particular disease to the frequency of disease in any rigid fashion.

First, much of the research supported and conducted by the NIH is basic in nature, and not disease-specific. Consequently, disease-specific research figures tend to understate the contribution of basic research to the understanding of disease development. Likewise, grant applications to carry out basic research are most often not in support of a specific disease. Basic research provides the fundamental underpinnings of research advances in our understanding of specific diseases.

Second, because of the interdependent nature of scientific knowledge, there is significant overlap among different areas of research, even when they are targeted. For example, money that is being used to study the AIDS virus and the immune system is generating results that are not pertinent simply to AIDS. The results that have come out of our intensive study of this virus

and the immune system that the virus attacks are relevant to many other diseases--many important diseases. The intense research in this area is having a ripple effect in many other areas of research that are important in autoimmune disorders, other infectious diseases, the design of vaccines, and an understanding of basic mechanisms of cell function.

Third, decisions on funding levels for the research on different diseases reflect a combination of judgments about scientific opportunity and national priorities. On the broadest level, we receive direction from Congress during the appropriations process and in periodic reauthorization legislation hearings to which you have referred. In addition, we obtain guidance from the Administration, and from the NIH constituent Institutes, Centers, and Divisions (ICDs) as well as various NIH advisory committees that form the decision making of the agency throughout the year. Through those channels of advice flow the many diverse viewpoints of the American people and of concerned groups about what research should receive priority for funding.

In addition to these directives and inputs regarding priority areas of research, NIH strives to allocate research funding on the basis of scientific advances and opportunities and to support the highest quality research as identified through the peer-review process. To that end, we support a substantial number of investigator-initiated proposals through grants to the extramural research community. In my view the greatest and most influential discoveries have usually been the products of young minds free to think creatively about the natural world. This is especially true in the basic research supported and conducted by NIH since tangible results of scientific inquiry cannot always be defined or planned in advance. Consequently, while society may desire that a specific goal be attained within a certain time frame such as a "cure for arthritis," a lack of knowledge regarding underlying psychological processes about the disease may need to be addressed before diagnostic and therapeutic technologies can be developed and evaluated. At the same time, a recent research advance in another area may create unplanned and unexpected new scientific opportunities for R&D, including further diagnostic and therapeutic applications.

Finally, as a public health agency, NIH regularly considers the critical public health threats of various diseases, such as AIDS and tuberculosis, in its research decisions and mobilizes resources appropriately to address these concerns.

To give you an idea of the funding amounts for specific diseases that are most often requested, I am providing the following table:

DHHS-National Institutes of Health
Research Initiatives/Programs of Interest
(Dollars in thousands)

Research/Disease Area	FY 1993 Actual	FY 1994 Actual	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate	Percent Change
1. Aging	\$748,773	\$782,017	\$820,187	\$859,082	\$875,521	1.91
2. Alzheimer's Disease	287,239	298,104	296,741	308,717	314,159	1.76
3. AIDS Research	1,073,957	1,296,471	1,333,380	1,407,824	1,431,908	1.71
Minority AIDS Research	196,960	252,329	255,488	265,430	267,354	0.72
Pediatric AIDS Research	144,633	169,329	161,794	166,027	163,267	-1.66
4. Arthritis	155,469	191,735	207,310	218,094	221,269	1.46
5. Batten's Disease	2,993	3,272	2,481	2,605	2,663	2.23
6. Biotechnology Research	4,233,040	4,314,200	4,598,065	4,820,381	4,903,645	1.73
7. Cancer Research	2,225,214	2,345,666	2,434,304	2,576,781	2,612,819	1.40
Breast Cancer	228,937	306,121	363,870	403,273	409,545	1.56
Cervical Cancer	48,035	47,556	53,882	55,735	56,689	1.71
Lung Cancer	93,689	120,626	123,237	126,742	130,430	2.91
Ovarian Cancer	34,319	36,854	39,095	40,382	41,322	2.33
Prostate Cancer	62,321	69,221	85,465	92,982	94,614	1.76
Colo-Rectal Cancer	77,808	87,749	102,371	105,561	108,364	2.66
Uterine Cancer	7,101	8,914	13,649	14,159	14,450	2.06
8. Clinical Trials	1,031,662	1,130,317	1,172,633	1,213,350	1,224,746	0.94
9. Contraception/Reproduction Research	148,176	152,016	171,036	178,780	181,737	1.65
10. Cystic Fibrosis	63,279	60,280	58,645	61,032	62,056	1.68
11. Diabetes	285,649	293,615	295,142	309,641	313,334	1.19
12. Diagnostic Radiology	182,767	188,164	195,434	205,448	211,677	3.03
13. Diethylstilbestrol (DES)	6,647	7,561	7,844	8,065	8,252	2.32
14. Epstein Barr Virus (Chronic Fatigue)	17,417 5,426	18,663 6,130	17,560 8,020	18,428 7,700	18,620 7,818	1.04 1.53
15. Gene Mapping	590,410	607,487	659,016	702,015	718,959	2.41
16. Gene Therapy	131,455	165,116	191,458	200,747	204,748	1.99
17. Head Injury	35,516	49,877	54,183	56,874	57,950	1.89
18. Health & Behavioral Research	833,213	776,060	809,177	840,373	854,749	1.71
19. Fetal Tissue Research	15,968	21,707	23,693	24,826	25,293	1.88
20. Hypertension	170,970	173,171	170,334	176,680	179,445	1.56
21. Immunology	959,616	999,478	1,046,381	1,092,233	1,108,272	1.47
22. Infant Mortality/ (LBW)	301,473	324,836	327,108	341,217	347,136	1.73
23. Interstitial Cystitis	7,991	8,980	8,918	9,000	9,100	1.11
24. Kidney Disease	188,684	191,264	192,196	200,938	203,677	1.36
25. Lead Poisoning	13,039	13,405	20,869	21,331	21,442	0.52
26. Lupus	27,346	29,509	31,162	32,683	33,380	2.13
27. Lyme Disease	11,235	15,498	13,447	14,026	14,313	2.05
28. Nutrition Research	373,250	400,701	409,685	431,317	438,734	1.72
29. Obesity	74,423	83,597	87,398	91,905	93,707	1.96
30. Osteoporosis	87,193	91,915	103,660	108,550	110,803	2.08
31. Pertussis Vaccine	14,428	7,587	6,004	6,274	6,393	1.90
32. Prevention (NCI Primary Prev.)	2,484,257 321,000	2,734,163 392,030	2,872,909 436,999	3,031,801 458,534	3,092,695 463,119	2.01 1.00
33. Rehabilitation	141,383	145,625	156,870	166,734	169,801	1.84
34. Rural Health	79,130	82,429	95,546	99,563	101,808	2.25
35. Schizophrenia	111,479	113,147	112,016	118,511	120,681	1.83
36. Sexually Trans. Diseases/Herpes	85,797	98,142	105,372	110,019	111,839	1.65
37. Sickle Cell Disease	44,839	54,305	53,948	55,765	56,719	1.71
38. Sleep Disorders	58,089	65,243	72,489	76,000	77,294	1.70
39. Smoking and Health	112,102	113,988	125,712	132,297	135,214	2.20
40. Stroke	106,771	112,377	114,296	119,450	121,543	1.75
41. Sudden Infant Death Syndrome	45,353	45,399	43,752	46,064	46,821	1.64
42. Topical Microbicides	9,200	12,284	21,344	23,200	23,844	2.78
43. Tropical Diseases	46,943	53,532	59,399	61,776	62,966	1.93
44. Tuberculosis Research	34,986	50,186	61,981	64,021	64,972	1.49
45. Urologic Diseases	152,121	163,970	199,320	214,946	217,036	0.97
46. Vaccine Development	220,465	258,133	273,174	285,960	297,045	3.88
Vaccine Related	253,344	294,726	299,750	314,426	325,791	3.61
47. Women's Health Research	1,286,395	1,479,359	1,632,205	1,725,236	1,753,096	1.61

SIRABIS1997SUM WK4

UPDATED: APRIL 15, 1996--Women's Health, Cystic Fibrosis, Diabetes

QUESTION FOR THE RECORD

Mr. Istook: I have heard reports about a number of people, I believe I heard it was 300 in France and some here in the United States, who had been HIV-positive but are now HIV negative. Could you please tell the committee (for the record if possible) what you know about how this was supposedly accomplished? We have heard that they reported the results to NIH. Please send their report and NIH's evaluation of their results.

Dr. Varmus: I believe you are referring to reports of infants identified as HIV-infected when they were born, but whose infection appears to have cleared. These cases were reported in the medical literature, but they were not directly reported to the NIH.

The case of a single infant was reported in the New England Journal of Medicine by investigators at UCLA. The evidence that the child was infected was provided by successful recovery of HIV at 19 and 51 days of age. However, by 12 months of age, the child was seronegative, and virus could no longer be cultured. That child is now five years of age and remains HIV-seronegative. A study published in the Lancet this year reported findings from research conducted at four sites of the European collaborative study of children born to HIV-infected mothers. Of the 264 children tested, six children were virus-positive early in life but later tested negative.

Scientists have met to review these instances of "transient infection," including an NIH-sponsored group. While the significance of these findings is not yet fully established, they are consistent with the development of immune responses capable of clearing the viral infection. More research is necessary, and the researchers are carefully following these children.

NIH continues to support research to determine the course of the disease following initial detection of infection. NIH also is following a larger population of children in clinical trials to determine whether specific therapeutic interventions can alter or halt the course of the disease.

Copies of their reports will be sent to the committee under separate cover.

QUESTIONS SUBMITTED BY CONGRESSMAN STOKES**HUMAN GENOME**

Mr. Stokes: To what extent does the human genome project fully incorporate the genetic variations among minorities?

Dr. Varmus: The NCHGR is very much aware of the importance of genetic variation and its role in health and disease. A number of projects are specifically directed toward minorities. For example, the intramural program of NCHGR is studying the genetic basis of diabetes in populations in West Africa that are particularly suitable for such investigations. The results will help us understand the genetic component of diabetes in U.S. African American populations.

The NCHGR's Ethical, Legal, and Social Issues (ELSI) program has a significant investment in research projects to develop models for assessing attitudes and delivering information about genetic testing for breast, colon and ovarian cancers in Native Americans, African Americans, Hispanics, and Native Hawaiians. There is also a project to understand Native Americans' attitudes toward a variety of ELSI issues with particular emphasis on concepts of privacy and decision making processes in an attempt to develop a culturally-sensitive model that can be used to deal with ELSI issues that will result from human genome research.

Mr. Stokes: What is the status of the gene repository as it related to African Americans and other minorities?

Dr. Varmus: The NCHGR does not have a gene repository on African Americans, other minorities or other populations. There are no plans for such a repository.

CLINICAL TRIALS MINORITY PARTICIPATION

Mr. Stokes: Clinical trials are critical to further advances in the treatment, diagnosis, and prevention of death and disease. What progress are you making with respect to recruitment and retention of minorities in clinical trials?

Dr. Varmus: For the very first time, NIH has developed a computerized tracking system to monitor demographic data on subjects in clinical research protocols. Baseline enrollment figures have just been compiled and are presently being analyzed. Although we cannot document any changes in enrollment on the basis of one year's data, it is clear that gaps in knowledge are being addressed through research.

Preliminary data released by the Office of Research on Women's Health showed that for 783 clinical studies conducted at the Warren G. Magnuson Clinical Center, approximately 49 percent of the patients seen in 1994 were women, 51 percent were men. Among minority subjects, representation in intramural studies was highest

for Black (not Hispanic) subjects (9.83 percent) and lowest for American Indian/Alaskan native subjects (0.24 percent).

Preliminary data for NIH extramural studies also showed that substantial numbers of women and minorities have been included as research subjects. Approximately 50 percent of the subjects in extramural studies were women, 46 percent men, and in 3 percent the gender is unknown. Among minority subjects, representation in extramural studies was highest for Black (not Hispanic) subjects (23.99 percent) and lowest for American Indian/Alaskan native subjects (1.02 percent).

The aggregate data will enable us, for the very first time, to obtain an initial measurement of inclusion so that we may begin to formulate more specific questions about any apparent gaps in enrollment. Data compiled in future years will allow for longitudinal examination of trends.

RECRUITMENT OF MINORITY RESEARCHERS

Mr. Stokes: What progress have you made since you were here last with respect to the recruitment and the involvement of African American, Hispanic and other disadvantaged populations in biomedical research, NIH planning and decision-making?

Dr. Varmus: Over the past year, the NIH has focused attention on improving the diversity in all occupations, with particular emphasis on scientific and senior level administrative positions. As part of this focus, a new affirmative action planning process was undertaken as a pilot to increase the pool of applicants recruited for employment as well as training and development programs. The pilot program takes into account substantial underrepresentation of EEO groups, the availability of such groups in the relevant job category or field of expertise, and the level of hiring the ICD anticipates. Depending on the career and grade level being reviewed, African Americans, Hispanics, Asians, Native Americans, and nonminority men and women continue to be under represented to some degree, especially in the sciences. With various downsizing and reinvention mandates, the available opportunities for increasing diversity are small.

The pilot program is in effect through FY 1996 and will be evaluated at the end of September. Since April 1995 when the pilot became effective, some modest progress is evident. Of the eight most populous (100 or more employees) scientific occupations, there no longer is severe underrepresentation of any EEO group in four of them. The four job categories where progress has been made are Biologist, Health Science Administrator, Chemist, and Medical Officer. While the NIH has not reached parity with availability data, severe underrepresentation has been all but eliminated for African Americans in the Microbiologist and Physical Scientist occupations; for Hispanics in the Pharmacologist and Physical Scientist occupations; and for nonminority women in the Psychologist, Microbiologist, and Pharmacologist occupations.

The NIH also sponsors two loan repayment/forgiveness programs to attract appropriately qualified health professionals, primarily physicians (MD's) and others with doctoral-level degrees, i.e. Ph.D.s, to NIH intramural research training positions. The AIDS Loan Repayment Program (LRP), implemented in FY 1990, seeks to recruit basic and clinical researchers to NIH's intramural research training programs. Through FY 1995, 85 researchers have participated in this LRP, 20 of whom were from underrepresented minority groups. Of these 20 AIDS-LRP participants, 11 percent were African-American and 9 percent were Hispanic. The underrepresented minority AIDS-LRP participants were employed by a variety of NIH's ICs, including ten from the National Cancer Institute (NCI), five from the National Institute of Allergy and Infectious Disease (NIAID), three from the National Institute of Neurological Disorders and Stroke (NINDS), one from the National Eye Institute (NEI), and one from the National Institute of Dental Research (NIDR). Health disciplines represented included: internal medicine; pediatrics; neurology; public health; pathology; ophthalmology; epidemiology; cellular biology; biochemistry; and dentistry.

Although there is no statutory mandate for the recruitment of African-American, Hispanic and other disadvantaged populations to the AIDS-LRP, the Office of Loan Repayment Programs (OLRP) has engaged in a variety of outreach and information dissemination efforts to attract qualified researchers from these groups. The OLRP has participated as both an exhibitor and presenter at the annual meetings of the Student National Medical Association, the National Medical Association, the Biomedical Science Careers Project, and the Minority Health Professions Foundation. Planned recruitment and information dissemination activities later this fiscal year include participation at the annual meetings of the Society for Advancement of Chicano and Native Americans in the Sciences and the National Coalition of Hispanic Health and Human Services Organizations.

The NIH also sponsors the Clinical Research LRP for Individuals from Disadvantaged Backgrounds (CR-LRP), which was implemented in FY 1994. This loan repayment program seeks to recruit health professionals from disadvantaged backgrounds to clinical research training positions within the intramural programs. Of the 19 participants awarded contracts since the program's inception, 16 hold M.D.s., two hold an M.D., Ph.D. and one holds a D.D.M., and 47 percent are female. The program's statutory mandate is to attract individuals from disadvantaged backgrounds, and in its recruitment efforts, the NIH has been successful in attracting disadvantaged individuals from the following groups: 52.6 percent African-American, 15.8 percent Hispanic, and 31.6 percent Caucasian. Underrepresented minority CR-LRP participants are employed by the following ICs: NCI (4); CC (1); NEI (1); NHLBI (1); NIA (1); NIAAA (1); NIAID (1); NIDCD (1); and the NIDDK (1).

The OLRP plans to continue to focus recruitment and information dissemination programs at potentially disadvantaged populations, by attendance at the national meetings referenced above, as well as place advertisements in *Medico Interamericano*, *Journal of the National Medical Association*, *Hispanic Magazine*, and the *Student National Medical Association*.

During FY 1996, NIH has filled the following high level appointments with candidates from underrepresented groups as follows:

FTP Senior Level Appointments
October 1995 - April 1996

Accessions:

Health Science Administrator	601	GS 14 1 Asian Woman, 1 White Woman
Medical Officer	602	GS 15 1 White Woman
Nutritionist	630	GS 15 1 White Woman
Architecture Specialist	808	GS 14 1 Black Woman, 1 Asian Man
Statistician	1530	GS 14 1 White Woman
Personnel Officer	201	GS 14 1 White Woman
Manager	301	GS 13 1 Black Woman
Management Analyst	343	GS 13 1 Black Woman, 1 Black Man, 3 White Women
Writer/Editor	1083	GS 13 1 White Woman
Accountant	510	GS 13 3 Black Women
Speech Pathologist	665	GS 13 1 White Woman
Chemist	1320	GS 13 1 Asian Man

Other Appointments:

Deputy Director, NINDS	Dr. Audrey Penn	Black Woman
Director, NINR	Dr. Patricia Grady	White Woman

The board completed an initial assessment of employee-nominees. Currently 31 employees have been approved for appointment in the SBRS.

MINORITY PARTICIPATION IN BIOMEDICAL RESEARCH

Mr. Stokes: I understand that less than one percent of the NIH budget awarded to our nation's historically black health professions schools. Given that African Americans and other minority suffer disproportionately from exactly the health problems that the NIH is designed to address, what initiatives are underway at the institute to improve the participation of historically black colleges and universities and Hispanic serving institutions in biomedical research from investigator initiated awards to research centers?

Dr. Varmus: At the National Institutes of Health, each institute and center (IC) supports initiatives designed to improve the participation of Historically Black Colleges and Universities (HBCUs) and Hispanic Serving Institutions (HSI) in biomedical research. In 1995, a total of \$81,978,450 was awarded to historically black and black plurality institutions. During 1995, \$65,605,533 was awarded to institutions having more than 25percent Hispanic enrollment.

Comprehensive reports describing each activity including the dollar amount of the award to the specific HBCU or HSI are available. Exemplary activities are listed below:

Through an intra-agency agreement with the Office of Research on Minority Health (ORMH), the National Institute of Neurological Disorders and Stroke (NINDS) is collaborating in the establishment of a Neuroscience Research Center at Morehouse School of Medicine. The Center brings interested researchers together to interact scientifically, and trains minority science majors in the neurosciences.

As a result of 1993 appropriations language in which Congress urged NIH to develop plans for addressing the clinical research infrastructural needs of minority medical schools, the Research Centers in Minority Institutions (RCMI) program of the National Center for Research Resources (NCRR) designed a new initiative: the RCMI Clinical Research Infrastructure Initiative (RCII). The first awards were made in FY 1995. Two of the four recipients were HBCUs: Charles Drew University of Medicine & Science and Morehouse School of Medicine. One recipient was an HSI: Universidad Central del Caribe.

The National Cancer Institute's (NCI) Comprehensive Minority Biomedical Program supports contracts to Texas Southern University and Meharry Medical college to explore approaches to building cancer prevention awareness in the African American community through HBCUs. The contracts are to implement model strategies for disseminating cancer information to African American populations through minority academic institutions, in particular the HBCUs. The NCI also supports the Drew/Meharry/Morehouse Consortium Cancer Center to conduct research aimed at reducing the high incidence and mortality from cancer in the black population.

The AIDS Infrastructure Initiative of the Research Centers in Minority Institutions (RCMI) Program seeks to expand physical facilities and faculty competence in virology, immunology, molecular biology, and the neurosciences so that minority institutions may join mainstream research on AIDS. Five HBCUs and three HSIs are participating in this initiative which is administered by the National Center for Research Resources. Also, to increase the participation of minority institutions in AIDS research, the National Institute of Allergies and Infectious Diseases (NIAID) supports "AIDS Clinical Trials Units at Minority Institutions" at Howard University, Meharry Medical College and the University of Puerto Rico.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a full-scale clinical trial entitled "African American Study of Kidney Disease and Hypertension (AASK)" to define the most appropriate antihypertensive regimen, as well as the appropriate level at which blood pressure should be controlled. Three HBCUs are participating in this activity.

FACILITIES CONSTRUCTION

Mr. Stokes: With respect to the NIH facility construction law, acknowledging the difference among institutions, and the fact that the law designates that 25 percent of extramural facilities funds for developing programs, -- is the peer review process so rigid at NIH that a developing institution such as, for example Florida A & M College of Pharmacy, be required to compete straight up against an institution for example like, the University of Pennsylvania or Johns Hopkins University?

Dr. Varmus: The NIH Revitalization Act of 1993, which authorizes the extramural facilities construction program, provides in Sec. 481A, subsection (c), paragraph (1) the review requirements for all construction applications received, including those received from Institutions of Emerging Excellence. Paragraph (3) of subsection (c) of the law states that "Of the amounts appropriated...the Director of the Center shall make available 25 percent for grants...to applicants that, in addition to meeting the requirements established in paragraph (1), have demonstrated emerging excellence in biomedical and behavioral research...." Clearly the intent of the authorizing language is that all construction awards be made under the program meet the same requirements.

These institutions can compete successfully with other, more established research institutions. This was proven the first year of the construction program when applications from two of these institutions scored well and were funded.

Mr. Stokes: Have the peer review panels reviewing the applications had adequate representation from developing institutions? Elaborate.

Dr. Varmus: Representatives from developing institutions are included on the peer review panels that review the extramural construction applications. In 1994, the panel included seven representatives from institutions of emerging excellence. In 1995, the panel included representatives from six institutions of emerging excellence. In addition to these representatives, the review panels for both years also included other minority representation.

WOMEN'S AND MINORITY HEALTH INITIATIVES

Mr. Stokes: The FY 1997 budget for the NIH reflect approximately an 8 percent increase over FY 1996 funding. However, no portion of that increase is shared with the women's health initiative and the minority health initiative. This sends an extremely negative message to both communities regarding your commitments to improve health, elaborate on this situation.

Dr. Varmus: The NIH and the Office of the Director (OD) places a high priority on both the Women's Health Initiative (WHI) and the Minority Health Initiative (MHI). The FY 1997 President's budget level for NIH represents an increase of 3.9 percent in total over FY 1996. Without the Buildings and

Facilities request, the budget proposal represents a 1.6 percent increase. The FY 1997 budget level for the OD is approximately 3 percent below FY1996. However, within the OD, funding for the WHI has been maintained at the FY 1996 level which will keep it on target and maintain the WHI timetable during the coming year. Funding for the MHI is nearly straight lined at \$62.6 million. FY 1997 funding levels for these two research initiatives are generally consistent with their previously determined long-range spending plans.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: For the diseases and disorders that are under the purview of your (Institute), where are we today with respect to closing the gap in minority health, specifically what progress do you have to report to the Subcommittee this year? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Varmus: It is encouraging to look at the human longevity statistics over the past two decades and note that the life expectancy of US citizens has increased. The average life expectancy of white females has increased from 76 to 80 years and white males from 68 to 73 years. The same time period showed a life expectancy of black females increasing from 68 to 74 years and black males from 60 to 65 years. However, this also tells the story of the health disparity between a minority and a majority population, both living in the same country with presumably the same opportunities for lifelong health care. It does offer evidence that biomedical research leading to better nutrition, better prevention measures and better health care, is having some effect on improving the health of our citizens, in general. This also makes another important point, that the benefits of biomedical research must be viewed over an extended time period, with a great lag between carrying out the research and observing the benefits to the general U.S. population. Our Nation's investment in pursuing the understanding of diseases and conditions that detract from long healthy lives of all Americans, must be seen as a long term effort. At the same time it behooves us to identify our major health problems now so that research efforts to solve these problems can begin as soon as possible.

The Office of Research on Minority Health (ORMH) at the National Institutes of Health (NIH), has as a major mission to collaborate with the NIH Institutes, Centers and Divisions (ICDs) in identifying and attacking health problems that affect our nations' minority citizens in a disproportionate manner. Once identified, the ORMH can provide additional funding to the ICDs to initiate new research programs which will rapidly begin the search for an answer to the health problems creating the greater suffering and shorter lifespan of our minority citizens.

Progress reported by the ORMH in reducing the health problems of minorities can be measured better by the initiation of new programs than by reporting an improvement in their health status. While the general improvement

in lifespan can be noted from the above data, specific health problems continue to need attention. When we observe infant mortality rates by race over the time period 1970 to 1992, we note a decrease from 18 to 7 deaths per 1000 live births in white infants and a reduction of 35 to 17 deaths per 1000 live births in black infants. While we are pleased with the general reduction in infant mortality we must note that the mortality rate for black infants was 2.4 times greater than for white infants in 1992. The ORMH and the National Institute of Child Health and Human Development (NICHD) have provided joint funding for several research efforts attending to the problem of high infant mortality rates in minorities. One study targets residents of Washington D.C. to examine infant mortality issues related to poverty, low maternal education, inadequate housing, barriers to access to prenatal care and adverse health behaviors as well as other factors. These studies attend to problems of both African Americans and Hispanics living in the inner city and involve six Washington D.C. medical institutions.

Another collaborative effort between ORMH and NICHD supports research on the behavior of minority youth. This research is on minority youth ages 10 - 18 as behavior is related to violence, injuries and deaths, the use of alcohol and drugs, and unwanted pregnancies and sexually transmitted diseases. The study involves a number of individual grants in different localities, involving African American, Hispanic, Native American and Asian youth. All involve community participation and will seek to identify effective methods of changing the destructive behavior through efforts to help the young people develop and practice skills in decision making, conflict resolution and in reducing their own risks of unhealthy outcomes. They will learn to use community resources and help to develop control over their own impulses and to understand and combat peer and media pressure to engage in unhealthy behaviors. Progress will not be measurable for several years as these are newly initiated projects.

Diabetes is another disease affecting minority citizens. The Hispanic and African American populations experience non-insulin-dependent diabetes mellitus (NIDDM) more frequently than Caucasian. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with the Centers for Disease Control and Prevention (CDC) and ORMH, has initiated a project to study education and group support for diabetic Hispanics in a community setting. It will provide instruction on diet, exercise and related topics in a group setting to study the most effective means of altering behavior conducive to the onset of NIDDM. Related studies involve NIDDK, CDC, ORMH and the National Institute of Child Health and Human Development (NICHD), in a study designed to develop modifications of behavior which have contributed to gestational diabetes among obese minority women, who are at a special risk. This seven year study began this year and will compare behavioral modification efforts including diet and exercise, with oral medication.

Cardiovascular disease and stroke have affected African Americans in a disproportionate manner and continue to be a leading cause of early death. Recently there has been success in the treatment of stroke in all Americans

through the use of tissue-plasminogen-activator (T-PA). With this therapy, excellent recoveries after three months increased 30-50 percent. This is heartening and will benefit all Americans. Hypertension, however, remains a problem related to cardiovascular disease and to end stage renal disease. The NIDDK and ORMH jointly initiated a program called African-American Study of Kidney Disease (AASK), to determine the most effective control of hypertension. The objective is to bring about the delay or to prevent the progression of renal disease to end-stage. The trial has begun and will recruit approximately 1000 patients in over 20 medical centers including the Meharry, Morehouse and King-Drew centers. The program was initiated in 1995 and these patients will be followed until the year 2000.

Chemical dependency is another major minority health issue priority. The National Institute on Drug Abuse (NIDA) has sponsored several projects in cooperation with ORMH to study the problems of drugs in our minority youth population. Some advances have been reported, such as through the study showing that over a 6 year period, drug use among 7th graders from 56 schools was reduced by the 12th grade by 44 percent, using a school based prevention approach which teaches health knowledge, drug resistance skills and general coping and social skills. Other cooperative projects are ongoing.

INVOLVEMENT OF MINORITY SCIENTISTS IN PLANNING

Mr. Stokes: To what extent has progress been made with respect to the involvement of minority scientists in NIH planning and decision making?

Dr. Varnus: Over the past year, the NIH has focused attention on improving the diversity of all occupations, with particular emphasis on scientific and senior level administrative positions. As part of this focus, a new affirmative action planning process was undertaken as a pilot to increase the pool of applicants recruited for employment as well as training and development programs. The pilot program takes into account substantial underrepresentation of EEO groups, the availability of such groups in the relevant job category or field of expertise, and the level of hiring the ICD anticipates. Depending on the career and grade level being reviewed, African Americans, Hispanics, Asians, Native Americans, and nonminority men and women continue to be under represented to some degree, especially in the sciences.

The pilot program is in effect through FY 1996 and will be evaluated at the end of September. Since April 1995 when the pilot became effective, some modest progress is evident. Of the 8 most populous (100 or more employees) scientific occupations, four no longer indicate severe underrepresentation of any EEO group. The four job categories where progress has been made are Biologist, Health Science Administrator, Chemist, and Medical Officer. While the NIH has not reached parity with availability data, severe underrepresentation has been all but eliminated for African Americans in the Microbiologist and Physical Scientist occupations; for Hispanics in the Pharmacologist and Physical Scientist

occupations; and for nonminority women in the Psychologist, Microbiologist, and Pharmacologist occupations.

This year the NIH is participating in a new pay system, the DHHS Senior Biomedical Research Service (SBRS). A policy board was created to evaluate NIH scientists and outside recruits for acceptance into the SBRS. The SBRS is looked upon as an excellent recruitment tool for increasing diversity. The SBRS expands salary levels and benefits as well as providing the flexibility of a portable retirement system. These incentives should make the NIH more competitive in recruiting the small pool of highly qualified scientists that includes white males, as well as women and minorities. The policy board that assesses candidate eligibility for SBRS is diverse in its make up.

OPPORTUNITIES FOR MINORITY SCIENTISTS

Mr. Stokes: To what extent does NIH processes and procedures offer equitable opportunities for minority scientists to propose NIH sponsored research, to help ensure participation in intramural and extramural research?

Dr. Varmus: At the National Institutes of Health, each institute and center (IC) supports initiatives designed to improve the participation of Historically Black Colleges and Universities (HBCUs) and Hispanic Serving Institutions (HSI) in biomedical research. In 1995, a total of \$81,978,450 was awarded to historically black and black plurality institutions. During 1995, \$65,605,533 was awarded to institutions having more than 25 percent Hispanic enrollment. Comprehensive reports describing each activity including the dollar amount of the award to the specific HBCU or HSI are available. Exemplary activities are listed below:

Through an intra-agency agreement with the Office of Research on Minority Health (ORMH), the National Institute of Neurological Disorders and Stroke (NINDS) is collaborating in the establishment of a Neuroscience Research Center at Morehouse School of Medicine. The Center brings interested researchers together to interact scientifically, and trains minority science majors in the neurosciences.

As a result of 1993 appropriations language in which Congress urged NIH to develop plans for addressing the clinical research infrastructural needs of minority medical schools, the Research Centers in Minority Institutions (RCMI) program of the National Center for Research Resources (NCRR) designed a new initiative: the RCMI Clinical Research Infrastructure Initiative (RCII). The first awards were made in FY 1995. Two of the four recipients were HBCUs: Charles Drew University of Medicine & Science and Morehouse School of Medicine. One recipient was an HSI: Universidad Central del Caribe.

The National Cancer Institute's (NCI) Comprehensive Minority Biomedical Program supports contracts to Texas Southern University and

Meharry Medical college to explore approaches to building cancer prevention awareness in the African American community through HBCUs. The contracts are to implement model strategies for disseminating cancer information to African American populations through minority academic institutions, in particular the HBCUs. The NCI also supports the Drew/Meharry/Morehouse Consortium Cancer Center to conduct research aimed at reducing the high incidence and mortality from cancer in the black population.

The AIDS Infrastructure Initiative of the Research Centers in Minority Institutions (RCMI) Program seeks to expand physical facilities and faculty competence in virology, immunology, molecular biology, and the neurosciences so that minority institutions may join mainstream research on AIDS. Five HBCUs and three HSIs are participating in this initiative which is administered by the National Center for Research Resources. Also, to increase the participation of minority institutions in AIDS research, the National Institute of Allergies and Infectious Diseases (NIAID) supports "AIDS Clinical Trials Units at Minority Institutions" at Howard University, Meharry Medical College and the University of Puerto Rico.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a full-scale clinical trial entitled "African American Study of Kidney Disease and Hypertension (AASK)" to define the most appropriate antihypertensive regimen, as well as the appropriate level at which blood pressure should be controlled. Three HBCUs are participating in this activity.

QUESTIONS SUBMITTED BY CONGRESSMAN HOYER**CLINICAL RESEARCH AND RESEARCH TRAINING REPORT**

Mr. Hoyer: Last year, the committee reports accompanying both the House and Senate bills asked that you move forward to Implement the recommendations of the Institutes of Medicine on clinical research. The subcommittees asked for a report by January 1 on the progress made. When can we expect that report?

Dr. Varmus: The report "Clinical Research and Research Training" was formally sent to the Committee by the Department of Health and Human Services on April 14, 1996.

Mr. Hoyer: Can you give us an idea of what it will contain?

Dr. Varmus: The report is as follows.

Department of Health and Human Services

National Institutes of Health
Office of Extramural Research

Clinical Research and Research Training

Progress Report Requested in
House Report Number 104-209

Harold Varmus, M.D.
Director, NIH
April 1996

INTRODUCTION

The House Appropriations Committee in House Report Number 104-209 stated:

"The Committee requests a report from the NIH Director by January 1 as to the progress NIH is making towards three initiatives recommended by the Institute of Medicine (IOM): the expansion of the General Clinical Research Centers program, the expansion of clinical research training opportunities, and the development of a loan forgiveness program for persons who pursue clinical research careers."

The following report has been prepared by the NIH for transmittal by the Department of Health and Human Services (DHHS) in response to this request:

GENERAL CLINICAL RESEARCH CENTERS PROGRAM

The National Center for Research Resources (NCRR) provides infrastructure for clinical research throughout the country through several programs, including the General Clinical Research Centers (GCRCs) program. The GCRC program provides infrastructure to academic institutions through the support of research nurses and dietitians, biostatisticians, computerized database management and analysis systems, sophisticated laboratories, inpatient and outpatient research facilities and other resources vital for state-of-the-art patient-oriented research. The GCRCs will continue to extend the range and intensity of clinical research by complementing funding provided to investigators from other components of NIH.

In fiscal year 1995, over 7,500 investigators at GCRCs carried out 5,351 clinical research projects involving 26,682 hospital admissions, 79,979 research inpatient days, and 245,016 outpatient research visits. To further expand clinical research capacity and activity in a cost effective manner, new satellite GCRCs have been established in both specialized and pediatric hospitals. Additional support will be provided in FY 1996 to further increase the patient research capacity of the network of GCRCs.

In addition, the NCRR works closely with the categorical institutes and centers of NIH to form partnerships to enhance clinical research and clinical trials. One recent example is the establishment of three National Gene Vector Laboratories through cooperative funding with the National Cancer Institute (NCI), National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK). These laboratories will produce and safety test clinical grade gene vectors suitable for clinical trials within the setting of the GCRCs and other sites. Cofunding and collaborations have also been established with the National Institute on Aging (NIA) and other governmental agencies, such as the National Aeronautics and Space Administration.

Due to the increasing impact of managed care on clinical research, GCRCs now provide support for more late Phase II and Phase III clinical trials as well as Phase I. Many GCRCs continue to be utilized for studies related to the Women's Health Initiative, the AIDS Clinical Trials Group, osteoporosis, neurodegenerative, behavioral, and rare disease research, along with many other areas.

CLINICAL RESEARCH TRAINING OPPORTUNITIES

Director's Panel on Clinical Research: Dr. Varmus has established a panel composed of leading representatives from government, academia, and industry to discuss the challenges facing health centers and investigators interested in patient oriented research. The Panel has established clinical research training as one of the major issues to be addressed. The Panel will analyze the quality and relevance of existing clinical research training programs, particularly in relation to the employment opportunities available to those who complete the training. This information will be used to generate recommendations that will enhance the quality of research training in clinical medicine at academic medical centers across our nation.

Intramural Initiatives: Under the direction of Dr. John I. Gallin, Director of the Warren G. Magnuson Clinical Center, the NIH has created a formal training program which includes a core curriculum in clinical research composed of four modules that cover scientific, ethical, legal, and social issues relevant to clinical research. The format of training includes didactic lectures, seminars, and practical exercises. An 8-week pilot program that enrolled 25 clinical associates from the intramural program has been successfully completed. In FY 96 the course was expanded to include 250 students and extended to run for a full academic year. Future plans include expanding course offerings through telecommunications and the World Wide Web as well as publishing and disseminating hard copies of the course content.

Clinical Associate Physician Program: To provide opportunities for the career development of physicians and dentists, NCRR has two ongoing supplemental programs to the GCRCs, the Clinical Associate Physician (CAP) and Minority Clinical Associate Physician (MCAP) programs which support young clinical research investigators for a period of up to three years. The number of CAP and MCAP candidates supported in mentor-supervised clinical research career development has steadily increased. In fiscal year 1993, 45 CAPs and 10 MCAPs were supported but support increased to 79 CAP and 19 MCAP awards in fiscal year 1995, reflecting the high priority for those programs. Recently, the GCRC Program has introduced a change in the submission policy, lifting the restriction on the number of submissions per center for the CAP and MCAP applications. It is expected that this change will lead to increased numbers of meritorious applications to be submitted and funded.

Clinical Research Scholar Program: Another new peer-reviewed pilot program, the Clinical Research Scholar (CRS) program, will be initiated by NCRR in 1996 to foster junior career development. The program will provide support for physicians and dentists who have an interest and aptitude for careers in patient-oriented clinical research but who have had limited clinical research training. The CRS

program will support the candidate for one year of course work and research activities in concert with an appropriate mentor who is a clinical investigator with peer-reviewed grant support. The first applications for the CRS program have been received and NCRR expects to make five to six awards.

Other GCRC Associated Research Training Activities: Within academic institutions with GCRCs, the GCRC staff with professional backgrounds in clinical research, experimental design, nutritional and nursing support, biostatistics, ethics, and computer systems management provide a focal point for training medical students and fellows as well as updating experienced faculty in new developments in clinical research. In several GCRCs, curricula include formalized lectures and hands-on research opportunities to learn new technologies for clinical research. Opportunities also exist for intense immersion in subjects related to patient-oriented research, bioethics, biostatistics and study design, including those for clinical trials.

Through these continuing efforts, the GCRC program and the clinical investigation staffs of the many diverse GCRCs provide extraordinary opportunities for all medical professionals interested in clinical research. In addition to the provision of academic, theoretical learning opportunities through lectures and seminars, medical professionals observe and participate in mentor-supervised clinical and laboratory studies, analyze data, prepare presentations and manuscripts, and learn how to prepare competitive applications for funding agencies. All of these steps are important in the preparation of young scientists for independent careers in clinical research.

LOAN FORGIVENESS PROGRAM

NIH Intramural Clinical Research Loan Repayment Program for Disadvantaged Investigators: As required in the NIH Revitalization Act of 1993 (P.L. 103-43) the NIH established a program of educational loan repayment to attract clinical researchers from disadvantaged backgrounds. The mission of the program is to recruit highly qualified health professionals from disadvantaged backgrounds to serve as clinical researchers, using the loan repayment as an economic incentive. The program may pay up to \$20,000 per year towards a participants outstanding eligible educational debts. Concurrent with the loan repayment, participants agree to conduct clinical research as NIH employees for a minimum of two years. At the current time, 19 physicians participate in this program and it is anticipated that an additional 10 physicians will be recruited if FY 96.

CLINICAL RESEARCH PANEL

Mr. Hoyer: I understand that you have appointed an advisory committee on clinical research. The Committee has met twice, and has yet to issue any recommendations. When will the committee next meet?

Dr. Varmus: The Clinical Research Panel was established with the intent of collecting all relevant data on Clinical Research activities and making

recommendations over a period of approximately three years. The third meeting of the Clinical Research Panel will be on May 16, 1996.

Mr. Hoyer: When can we expect a preliminary report from the Committee?

Dr. Varmus: The writing of a preliminary report will begin this summer when sufficient data has been collected, and will be discussed at the November 5, 1996 meeting of the Clinical Research Panel with the intent of having a preliminary report available for presentation to the Advisory Committee to the Director in December, 1996.

PROGRESS ON RETT SYNDROME TREATMENT

Mr. Hoyer: I understand that, in this Decade of the Brain, some of the most exciting advances in our scientific understanding have come in the areas of neurological disorders. Could you describe for me the progress which you have made in this area and its possible implications for a treatment for Rett Syndrome, a neurological disorder which affects primarily little girls?

Dr. Varmus: The Decade of the Brain has had a significant impact on our understanding of brain function, development and neurological disorders through the integrated support of basic, clinical and behavioral research. Just in the past year, investigators supported by NIH have discovered the genes for ataxia-telangiectasia, Friedreich's ataxia, one form of epilepsy, and two forms of Batten disease. Other advances have established the importance of folic acid in the prevention of birth defects, including spina bifida, and the role of excessive doses of Vitamin A in pregnancy in other type of birth defects. Preliminary evidence that the administration of magnesium sulfate to prevent premature labor may be related to a decreased incidence of cerebral palsy has sparked interest in further research by NIH and a number of outside groups.

In the area of basic research, scientists have begun to answer one of the most fundamental questions in neurobiology--how do nerves develop and travel long distances to reach their targets of action? Recently there has been substantial progress in understanding the molecules that guide these travels. They include both short-range (cell-to-cell contact) and long-range (diffusible) signals. Progress in neurodevelopmental disorders such as Rett's will build on this progress in genetics and neurodevelopmental research.

National Institute of Child Health and Human Development (NICHD) has been particularly focused on developmental processes and disorders that impact on young children. NICHD has supported international research meetings, two large program projects, and other research activities on Rett Syndrome in order to develop clinical strategies for the diagnosis, treatment and management of this disorder. NICHD is also making available Rett patient material through its Brain and Tissue Banks for Neurodevelopmental Disorders. In a larger context, NICHD continues to support research in mental retardation and developmental disabilities, behavior, and

developmental neurobiology, which also contribute directly and indirectly to Rett Syndrome research.

Two large interdisciplinary research programs supported by NICHD (Kennedy-Krieger Institute/Johns Hopkins Medical Center and Baylor College of Medicine) continue to make progress on the genetics, neuropathology, and clinical management of this disorder. Each program project brings together established investigators with expertise in brain neurochemistry, neuropathology, molecular genetics, brain imaging, and clinical psychology. These efforts have received continued support from families through the International Rett Syndrome Association.

Although we still lack a clear genetic or biomedical marker for early diagnosis, over the last few years we have made steady progress in understanding the genetics and neuropathology of Rett Syndrome. These studies have drawn on expertise from related fields of neurobiology and molecular genetics, which are supported by several institutes across NIH.

To date, Rett has defied the traditional genetic approaches that have provided dramatic breakthroughs in other neurological disorders, but we are fortunate to have some top molecular geneticists focusing their attention on Rett, in search of the mechanisms and chromosomal regions that are involved in the neuropathology of this disorder. The identification of the Rett gene will provide direct insight into the functional defect.

Other studies have focused on the neuropathology of Rett. Neurochemical and brain imaging studies reveal alterations in the neurotransmitters dopamine, acetylcholine, and glutamate in specific brain regions, which would account for the movement disorders, cognitive deficits, and seizures associated with Rett. These neuropathological findings, which are vaguely reminiscent of Parkinson and Alzheimer diseases, could lead to the development of pharmacological interventions to aid in the management of Rett Syndrome. In terms of the underlying deficit, some studies suggest that specific trophic factors may be lacking in the early brain development of children with Rett. The isolation and characterization of neurotrophic factors is an area of intense research in the neurosciences. Thus, Rett syndrome is now considered to be a disorder of early neurodevelopment rather than neurodegeneration.

Nutritional studies continue to show that high-energy, high-protein supplements result in improved growth and metabolism in girls with Rett. These approaches have been effective in increasing weight gain and delaying the physical wasting that typically occurs in the later stages of this disorder.

NICHD has taken the several steps to specifically promote research on Rett Syndrome. The disorder was highlighted in recent program announcements. Program staff continues to work with specific Rett researchers and clinicians to develop and refine their research proposals for NIH funding. NICHD is developing broad multidisciplinary initiatives in the area of autism research, and this could help in managing the autistic-like behaviors that are common in girls with Rett syndrome.

NICHD is also promoting the development of animal models for the study of neurodevelopmental disorders. This could be particularly important for understanding the specific pathophysiology of Rett and its effects on brain function, as well as piloting safe and effective clinical interventions.

HEALTH WEEK

Mr. Hoyer: As part of your public education effort, the NIH recently funded two pilot episodes of Health Week, a Maryland Public Television news show about medical research and its applications. I am excited about this partnership between the NIH and public television, and particularly Maryland Public Television, which has been an innovative and extremely successful public educator. Can you elaborate on your partnership with public television for the Committee?

Dr. Varmus: The Health Week partnership with Maryland Public Television (MPT) continues to be vigorous and optimistic. The NIH and MPT share the subcommittee's excitement in the potential of this program to educate and inform the American public. Though the NIH cannot participate in fundraising activities, it has suggested to MPT a wide range of potential funders in the corporate, foundation, and non-profit sectors. In addition, the NIH stands ready to assist MPT in educating potential funders about the scope, mission and accomplishments of the NIH. If funding is achieved, Health Week would perform a unique public service by providing reliable, research-based health information in a timely and attractive "TV magazine" format. MPT has recently received the seal of approval on Health Week from the Public Broadcast Service (PBS), which means that upon surety of funding, the PBS will offer it under their logo as a nationally broadcast program to the 350 member PBS stations. That will bring the NIH into full partnership with all those PBS stations who choose to broadcast Health Week across the Nation.

Mr. Hoyer: Does the NIH have further plans to utilize this medium for public education?

Dr. Varmus: NIH has made use of the public television medium through participating, over the years, in many of the science and health education programs produced for this medium. We plan to continue in that role, and to consider the many options presented by the rapid merging of television, Internet, and other telecommunications media. Obviously, if Health Week takes off, it will provide a unique opportunity for NIH to more fully exploit the educational and informational opportunities that this telecommunications merger presents.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Overview

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**The Department of Health and Human Services
The Public Health Service
National Institutes of Health**

**FY 1997 CONGRESSIONAL JUSTIFICATION
OVERVIEW**

INTRODUCTION

The National Institutes of Health (NIH) is the world's preeminent research institution dedicated to the support of science inspired by and focused on the challenges of human illness and health. The NIH comprises 24 institutes, centers, and divisions whose research activities extend from basic research that explores the fundamental workings of biological systems, to studies that examine pathology and treatments in clinical settings, to population-based analyses of health status and needs. The NIH research institutes that are focused either on a disease (e.g., cancer) or a primary organ system (e.g., heart, lung, and blood) are, to many Americans, the "visible" NIH. Yet, no less essential to the Nation's health are NIH programs that attend to overarching scientific needs and opportunities, such as deciphering the human genome, understanding cellular and tissue biology and physiology, training investigators in relevant scientific fields, and developing the array of technologies dictated by the needs of cutting-edge research — scientific improvisations that often move into clinical practice and enhance the capabilities and quality of routine medical treatment.

The NIH today represents a uniquely American process and triumph. Although the institution's roots extend back over a century, the "modern" NIH dates from the years following World War II when growing awareness of public health needs converged with new scientific capabilities, and an optimistic Nation gave the green light to a substantially increased national investment in health-related science. More than \$8 out of every \$10 dollars appropriated to NIH flows out to the scientific community at large; of these funds, the lion's share supports individual scientists. This "extramural" system is premised on *independence*, embodied in "investigator-initiated" research; on *self-governance*, embodied in peer review of scientists by scientists as the primary basis for judging the merits of research proposals and awarding funds; and on the powerful incentive of *competition* among the most highly trained scientists in the world. In 1996, the extramural research community numbers more than 50,000 investigators affiliated with some 1,700 university, hospital, and other research facilities located in all 50 states, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and points abroad. A small percentage of funds — approximately 10 percent of the budget — supports a core program of basic and clinical research activities administered and staffed by NIH's own physicians and scientists. This in-house, or intramural, research program houses the NIH Clinical Center and other resources that provide scientific, clinical, and educational services to the citizens of the U.S. and the world.

By any available measure — the extraordinary array of medical and health care options that NIH-funded research makes possible to the Nation; the number of Nobel Prizes brought home by NIH-sponsored scientists; the frequency of requests from scientists in every country of the world to train under the NIH aegis; the intellectual and financial vigor of U.S. biotechnology and

pharmaceutical firms, which are able to exploit the basic knowledge amassed by NIH; and, most importantly, lives saved through research — the successes of this public investment in NIH are indisputable.

The following introductory pages offer a brief overview of the range of scientific accomplishments, programmatic challenges and opportunities, and policy considerations that underlie the NIH Fiscal Year 1997 budget request.

STORY OF DISCOVERY

How Discoveries Come About

Unlike a TV detective show that is built around a clue, a high speed chase, and an exciting confrontation and resolution, problem solving in medical science is long, hard work, and "breakthroughs" come few and far between. More often than not, information accumulates over months and years, not hours and days. The story of spinal cord injury reveals that no single scientific Columbo stepped forth with an answer, but that hundreds of investigators worked as a team to generate information that today is crucial to the quality of life experienced by a quarter million Americans who have sustained devastating spinal injury...

A playground fall. A car accident. A foot misplaced on a ladder rung. A gunshot. Every 44 minutes or so, someone in the United States suffers a permanently disabling spinal cord injury. It is among the most unpredictable of medical crises, but, until recently, a victim of spinal cord injury could foresee a future unfolding at the moment of trauma that was all but too predictable — a future marred by immobility and dependency. This tragedy also has a dramatic lifetime effect upon family members and others.

The specter of such a future was, ironically, a modern development. Until the middle of this century, people who survived the immediate aftermath of spinal injury invariably succumbed rapidly to infection or respiratory failure; very few survived to endure chronic disability. But the discovery of antibiotics, the invention of respirators, and a growing availability of sophisticated emergency medical services allowed many more people to survive.

Just within the past 5 years, thanks to the persistence of a nationwide team of NIH-funded scientists and the willingness of thousands of patients to take part in research, important advances are being realized in this area. Through their efforts, emergency room doctors obtained, in 1990, a powerful new treatment: massive doses of the anti-inflammatory steroid *methylprednisolone*, given in the first hours after injury. This function-preserving treatment only exists because of years of NIH-sponsored basic research into the mechanisms of neuronal destruction in animal models of spinal trauma, and the large clinical trials with spinal injury patients.

Basic research on neuronal damage accelerated some three decades ago, sparked by the growing number of permanently disabled survivors of injury. Early on, it was clear that even injuries that did not actually sever spinal neurons often resulted in loss of all motor function below the site of

damage. In the mid-1960s, NIH established a research program to study spinal trauma, which funded many detailed anatomical and physiological studies of spinal injuries in animals. These basic studies revealed that many neurons survive the initial injury only to die in the subsequent hours or days. By the mid-1970s, researchers had shown that much of the secondary damage was the result of "friendly fire" incurred by immune and inflammatory responses to injury, as well as from the effects of highly reactive, short-lived molecules called free radicals, which form in the damaged spinal cord cells. Many of these factors play a part in late repair and cleanup of the injured tissues, but are excessively produced in the early phases of injury and themselves cause injury.

On the basis of the newly-acquired theoretical rationale for the use of anti-inflammatory drugs — which were known to limit the inflammatory response from the immune system — NIH embarked in 1978 on the National Acute Spinal Cord Injury Study (NASCIS) to test *methylprednisolone*. The clinical trial was conducted at 10 clinical research centers for spinal injury research at universities throughout the country, these had been organized by NIH in the mid-1970s to create a "critical mass" of basic researchers and clinicians focusing on this issue.

The results of the NASCIS trial, published in 1983, were disappointing. At the doses used, *methylprednisolone* therapy clearly did not significantly improve outcomes after spinal injury. The following year, the use of *methylprednisolone* in spinal injury was discontinued as a standard treatment.

Yet, positive results from animal studies in the early 1980s suggested that anti-inflammatory drugs might be effective in treating spinal cord injury, if used at much higher doses than those tested in the NASCIS trial. NIH-funded researchers found that in experimental animals ultra high doses of *methylprednisolone* — up to ten times those used in the NASCIS trial — block neuronal damage and, most importantly, limit the loss of motor function after injury.

These insights prompted a second large NASCIS trial, begun in 1985, to compare the use of ultrahigh doses of *methylprednisolone* to standard therapy. Initial results were so encouraging that in 1989 NIH issued a special clinical alert to all emergency physicians recommending a 24-hour ultrahigh dose *methylprednisolone* regimen, to be started within eight hours following spinal injury.

For many spinal injury patients, the long quest for answers proved most welcome. Limitation of secondary neuronal damage through early *methylprednisolone* treatment preserves about 20 percent of function that otherwise would be lost forever. Even small gains in retained function can make the difference between needing a respirator and breathing unassisted, for example, or between incontinence and bladder control — factors that determine how independent and productive a spinal injury survivor's life will be. However, these achievements, while important, are not enough. Scientists are pushing ahead to achieve more effective treatments. A third large clinical trial testing terilazad methylate, a promising new non-steroid drug that blocks free-radical damage, recently has been completed, and results are expected soon.

The basic knowledge and neuroprotective strategies pioneered in treatment of spinal injury are being applied in an attempt to control the destructive mechanisms of chronic neurodegenerative diseases such as Alzheimer's and Parkinson's. In addition — and perhaps most hopefully — a next wave of research now is underway into the factors that govern neuronal re-growth in the spinal cord, offering the hope that doctors will, some day, be able to roll back damage from spinal cord injury and allow people to recover increasing amounts of their lost functions.

OVERVIEW OF SCIENTIFIC ACCOMPLISHMENTS

The "Story of Discovery" illustrates that incremental advances, or step-by-step progress, are the rule, not the exception, within every compartment of NIH's broad range of research activities. Research news that earns TV coverage and newspaper headlines typically is the most apparent aspect of a multi-year effort that has involved many investigators, often in disparate fields, who may not have known of the specific clinical problem to which their piece of a solution ultimately would apply. In some cases, the hypothesis that led to a particular research project may prove wrong. However, a disproved idea may serve as the foundation for a new and, ultimately, ground-breaking finding that leads to a new treatment. In the past year, NIH scientific advances have ranged from insights into fundamental biology to the development of new therapeutic and preventive strategies. Each advance has a rich history of science behind it, and in many cases, a future of clinical application ahead of it.

Genetics

Basic research, which leads to fundamental discoveries about life processes, is the foundation for virtually all progress in the diagnosis, treatment and prevention of disease. Information being pieced together today presages radical changes in the ways we think about illness and health and in the capacities — already being felt — to treat and prevent illness, and to promote health. Some of the genes that are passed from parent to child determine whether a person will have a particular disease, have a susceptibility to it, or perhaps be protected from the risk of ever acquiring it. Genes can be likened to "instructions" which are written in the language of DNA. These genetic "instructions" provide the detailed information our cells need to build proteins. Proteins, in turn, control nearly every system in our body. Thus, if a particular section of our inherited "instructions" contains a mistake (mutation), then the protein produced according to those "instructions" may be defective. Whether the consequence of such a genetic mistake is a disease depends on how important the protein is and how severe the mistake. For example, the development of cystic fibrosis is the result of a single defective protein. Not all instances of disease are so clear cut, however. Many diseases are more complex, involving the interplay of many genes and their protein products, and the impact of diverse environmental factors as well.

Recently, a number of genes that play important roles in various disorders have either been isolated or identified. This identification is essential to further understanding of disease mechanisms and the development of new therapies for these disorders.

Alzheimer's Disease — NIH scientists have recently identified two genes, PS1 and PS2, that play a role in this devastating disease. Defects in either of these genes may be responsible for up

to 80 percent of a subtype of Alzheimer's that strikes before age 65. In searching for the functions of the proteins coded by the genes, investigators have detected a similarity between the PS1 and -2 proteins and a protein that is known to be involved in cell to cell communication and development. Accumulating evidence of the unexpectedly influential role of genetic factors in Alzheimer's disease adds urgency to the task of clarifying the molecular basis of the disease. In the interim, information about mutations in Alzheimer's-related genes likely will lead to diagnostic tests for at-risk members of affected families. Alzheimer's disease affects 4 million Americans today; that number will increase dramatically as baby boomers hit the age of highest risk.

Ataxia Telangiectasia (AT) — Researchers isolated the gene for AT, a rare disease of childhood that typically leads to death before adulthood. The disease is marked by progressive loss of coordination beginning between 1 and 2 years of age, growth retardation, immune deficiencies, high rates of cancer, radiation sensitivity, and premature aging. Although both parents must contribute a defective AT gene for a child to be affected, carriers — persons with one copy of the gene but who do not have the disease — are at increased risk for cancer and are highly sensitive to radiation. Identification of the gene paves the way to not only develop tests for prenatal diagnosis, but also to identify carriers, thus enabling carriers to choose to limit their use of radiation in cancer screening and treatment. Up to 8 percent of all breast cancers may be caused by mutations in the AT gene.

Breast Cancer — In an extension of the exciting 1994 finding of **BRCA1**, a gene that confers susceptibility to breast cancer, NIH scientists and collaborators discovered a specific mutation in the gene in nearly 1 percent of blood samples collected from women of Ashkenazi Jewish descent. This finding identifies a particular subgroup of the general population that may benefit from genetic testing for the BRCA1 mutation. Epidemiologists have hypothesized that this mutation may account for as much as 16 percent of breast and 39 percent of ovarian cancers among Ashkenazi Jewish women age 50 and under. The finding of the BRCA1 mutation within a discrete population makes consideration of genetic screening economically practical, and suggests the feasibility of targeted intervention and prevention efforts. In 1995, in this country alone, 182,000 new cases of breast cancer were diagnosed and 46,000 women died from the disease. Costs of breast cancer exceed \$12 billion per year.

With the scientific spotlight focused on the BRCA genes in the wake of the 1994 discovery of BRCA1, researchers last year discovered a "relative" of the gene that appears also to predispose women to inherited breast cancer. The newly isolated **BRCA2** gene may account for at least one-third of all cases of the disease. The function of the gene, which is found on chromosome 13, is not known; however, its DNA sequence suggests that it is related to BRCA1, which scientists believe produces a secreted protein that acts as a tumor suppressor. Defects in BRCA2 could cause the gene to fail to produce such a tumor suppressing protein, or to "misplace" it within a cell, rendering it ineffective. Either error could contribute to cancer. Ongoing research into the functions of these genes will increase our understanding of the genetic causes of breast cancer and promises to lead to improved screening tests and treatments.

Obesity — Basic researchers have made significant progress in unraveling the molecular and physiological basis of obesity and its links to diabetes and other diseases — a significant achievement, given that approximately 58 million Americans are overweight and consequently at increased risk for developing diabetes, cardiovascular disease, hypertension, gallbladder disease, and certain forms of cancer. Annual health care expenditures for obesity have been estimated at close to \$70 billion, with an additional \$30 billion or more spent on ineffective treatments and diet products. In recent research, NIH-supported scientists used a special strain of overweight mice as a model system for studying obesity. After identifying the *obese* gene in mice, they found its counterpart in humans. As a next step, scientists isolated the protein produced by the *obese* gene, a hormone they named leptin. They learned that the *obese* gene is active in fatty tissue, where it causes leptin to be secreted into the bloodstream. Leptin functions in regulating food intake by signaling the appetite-control area of the brain as to the levels of body fat.

Most recently, NIH-supported investigators identified important links between obesity and diabetes. They studied several special strains of mice and rats that were overweight and often developed diabetes. The mice had defective genes known as *diabetes* and *obese* and the rats a mutated gene called *fatty*. Researchers found that the animals are defective in a hormonal mechanism that controls eating. This mechanism allows the animals, and presumably humans, to regulate eating through the brain's response to a hormone, called leptin, that is produced from the *obese* gene in fat cells. Scientists further determined that the mouse *diabetes* gene and the rat *fatty* gene are identical and produce a protein that functions as the receptor for leptin. Although it appears unlikely that leptin itself is deficient in a significant number of obese individuals, the isolation of the genes for leptin and the leptin receptor has already deepened our understanding of metabolism and stimulated additional fundamental research.

Obesity is increasingly being understood as a chronic condition that is due to complex interactions of genetic, environmental, behavioral, and cultural factors. Genetic discoveries have opened the door to new studies of the mechanisms of appetite regulation, factors involved in the growth and regulation of fatty tissue, and the role of genetic and environmental interactions in obesity and diabetes. This work may eventually lead to more effective medical therapies for weight problems and help to reduce the prevalence of many chronic obesity-related diseases.

Human Genome Project — The human genome — the master instruction manual that contains all the genetic information needed to “build” a human being — has been likened to a three billion piece jigsaw puzzle. Only a decade ago, assembling such a puzzle was a scientific pipe dream. But recently, a three-year effort by more than 50 U.S. and French scientists culminated in the construction of a detailed “physical” map of the genome. The map contains more than 15,000 unique, identifiable DNA markers that allow researchers to orient themselves within the genome. The scientists faced enormous technical challenges in constructing the map; in fact, the first year and a half was spent devising a machine that could run 150,000 simultaneous reactions to amplify fragments of DNA. The team also had to design and develop an information management system for tracking and integrating the enormous amount of data produced by teams working simultaneously at multiple research sites around the world. Although an even more detailed physical map will be needed in order to complete the assembly of the genome puzzle, the new map in effect enables scientists to partition the immense mound of the puzzle's

pieces into smaller more manageable sections. In the short term, this first cut also provides a key tool for determining that disease genes are located on specific chromosomes. The new physical map is up on the Internet, and researchers around the world already are using the information. Recently, scientists have taken the next exciting step by beginning to actually sequence the human genome.

Brain Research

In this "Decade of the Brain," NIH scientists are making extraordinary progress in explaining how the brain works — and are beginning to understand how and why its failure to work properly can contribute to severe mental illnesses and neurological disorders. Brain research underscores the importance of parallel studies into the basic mechanisms of behavior, for brain and behavior are inseparably entwined. The following are just a few of the advances in brain research made in the past year.

The capacity of a developing nervous system to establish precise one-on-one connections among billions of nerve cells is as awesome as it has been mysterious to brain scientists. In an achievement that unravels a bit of the mystery, NIH-funded scientists recently discovered a group of proteins named *netrins* that act as long-range guidance signals for sprouting nerve cells during development. The discovery that netrins are strikingly similar to a protein in the roundworm suggests the importance of netrins throughout evolution and provides a simple animal model for examining the role of netrins in developmental processes. Information about how netrins work to guide new nerve cell projections may lead to treatments for regenerating nerves after injury and refined methods of nerve grafting and transplantation.

A research finding that attracted enormous attention in the popular media last year concerned scientific documentation that men's and women's brains work differently. The research in question used magnetic resonance imaging, or MRI, to observe activation of specific brain regions when male and female research participants performed several tasks involved in reading. The MRIs revealed that, in men, the left side of the brain was active during the performance task; in women, both sides were activated. In light of a 20 percent rate of reading disabilities that is spread equally among boys and girls upon entry to school, the research is especially significant in that it may help to explain why females are better able to compensate for reading difficulties. The findings may aid in designing remedial interventions that are gender specific.

Stroke

Even the most fundamental research supported by NIH is inspired by questions about biological events that ultimately play a role in illness and health. New treatments for a wide variety of diseases are built upon years of basic research into normal physiologic mechanisms as well as disease states. For example, extensive NIH-supported laboratory research on the mechanism of blood clotting contributed to the development of clot-dissolving drugs such as t-PA. This drug has been successfully used in treating heart attacks triggered by the formation of blood clots. Now this research and its applications may have important implications for stroke.

Four out of five strokes that are suffered by a half million Americans each year are caused by a blood clot that blocks blood flow to the brain. With the brain starved of oxygen and other nutrients, damage follows quickly and often with devastating effect. Researchers now have shown that the clot-dissolving drug t-PA is an effective emergency treatment for this type of stroke when given within 3 hours of initial symptoms. Clinicians feared that the drug, so useful in treating heart attacks, would cause the brain to hemorrhage, but rigorous clinical trials showed this risk was small among patients whose strokes were caused by blood clots. Among stroke victims who were administered the drug, the proportion who made excellent recoveries after three months increased by 30-50 percent. Given the narrow window for administering the drug after a stroke, the challenge now is to alert physicians about the finding and, more critically, educate the public about the symptoms of stroke and the importance of seeking emergency help.

Prevention

Rising health care costs highlight the importance of research that seeks to prevent disease before it strikes and to minimize the impact or the after-effects of illness and injury. In the quest for effective and efficient means of disease prevention, knowledge about basic mechanisms of illness and health must be complemented by thorough vaccination programs and public education aimed at health promoting lifestyles. Because some of these imperatives lie outside a research purview, NIH actively seeks the participation of private industry and the health care delivery sector in efforts to translate the products of science into health care practice.

Collaborations involving NIH-supported scientists, vaccine manufacturers, and investigators around the world recently have made available a new class of vaccines for pertussis, or whooping cough, a disease that each year claims 350,000 lives worldwide, primarily infants. The pertussis vaccine type that has been the "gold standard" for nearly 50 years is made from whole, killed pertussis-causing bacteria. It is extremely effective, but has been associated with adverse effects more frequently than any other vaccine in general use for infants. Many years of collaboration between NIH-supported basic scientists and the pharmaceutical industry led to the development of so-called *acellular* pertussis vaccines that use parts of pertussis bacteria instead of the whole organism. NIH-supported trials in Sweden and Italy now have demonstrated that three new acellular pertussis vaccines markedly reduce the frequency of side effects without diminishing the vaccines' efficacy.

NIH intramural scientists recently developed and patented the first vaccine against rotavirus, the cause of infections that annually result in an estimated 130 million episodes of diarrhea in infants and children. Moderate to severe dehydration occurs in 18 million of these episodes, and more than 870,000 youngsters from around the world die as a consequence. Rotaviral infections incur expenses of \$500 million annually in the U.S. in direct medical costs due to doctor visits and hospitalizations. The new vaccine protects against four different strains of human rotavirus. Clinical trials have shown the vaccine to be safe and to achieve significant reductions in the incidence of rotavirus diarrhea. It is 80 percent protective against severe rotaviral disease, and completely effective in preventing dehydrating illness. Routine childhood vaccination against rotavirus could alleviate this major public health problem immediately.

The importance of a healthy diet during pregnancy is widely acknowledged, less well-appreciated, however, are the benefits and risks associated with intake of *specific* nutrients. Painsstaking research by NIH-supported investigators now is elaborating the meaning of "healthy diet" for mother and developing fetus. Research earlier demonstrated, for example, that low levels of the B vitamin folic acid were implicated in neural tube defects such as spina bifida. As a result of findings from these and other studies, including a national health and nutrition survey, the Food and Drug Administration will soon require that enriched grain products be fortified with folic acid. This will help women of childbearing age achieve levels of folic acid sufficient to prevent neural tube defects. Other research suggests that high levels of certain vitamins can have harmful effects. For instance, previous animal studies indicated that high levels of vitamin A (retinol) may play a role in birth defects. Investigators recently confirmed this in humans. Children born to women who consumed high levels of vitamin A before their seventh week of pregnancy have a higher-than-normal incidence of birth defects of the face, head, thymus, heart, and brain. The infants of women who consumed vitamin A supplements at levels near the recommended daily allowance (RDA) had no increased risk for birth defects. Because a single capsule of some vitamin supplements available over-the-counter may exceed the RDA of Vitamin A for pregnant women, and because the vitamin is stored in the body, women consuming high levels of the vitamin may be affecting their babies before they know they are pregnant, causing damage in the first critical weeks of pregnancy. Increased public education on this issue offers simple and cost-effective opportunities for preventing one cause of birth defects.

Targeting preventive health interventions to at-risk individuals, as opposed to the general population, permits efficient use of health care dollars, a consideration that will assume increasing prominence as baby boomers age. Today, often preventable disability¹ among older Americans is a major reason why more than \$108 billion is spent annually on long-term care in the U.S. Researchers understandably are assigning high priority to studies that will identify risk factors for disability; predict disabling events; sharpen screening processes to identify target populations; and design and evaluate interventions specifically for individuals at risk for disability, such as the elderly. And the research is paying off:

- Three short tests of physical performance abilities could strongly predict incident-related disability as much as four years in advance.
- Older persons with three selected risk factors — such as mental impairment, low physical activity, and foot problems — are nearly 8-fold more likely to be involved in automobile accidents or moving violations compared to those with no risk factors.
- Research showed a 44 percent reduction in serious falls among older persons through the use of interventions focused on physical risk factors for falls such as bone fragility, muscle weakness, use of sedatives or multiple medications, and balance and walking problems.
- Patients treated on a special hospital unit for elderly persons focusing on rehabilitation, prevention of disability, and preparation for the patient's return to home were significantly more able to perform basic activities of daily living and less likely to need institutionalized long-term

¹"Aging Research: Practice, Promise & Priorities," NIH Publication No. 94-3696 (Bethesda, MD: National Institutes of Health, March 1994.)

care when they were discharged than individuals receiving standard hospital care. This was accomplished without increasing in-hospital or post-discharge costs.

Approaches to HIV/AIDS

AIDS is now the leading cause of death among Americans aged 25-44. As of June 30, 1995 nearly 500,000 cases of AIDS had been reported in the United States and 3.5 million world-wide.

HIV/AIDS poses an unprecedented challenge to medical science. The course of HIV infection is so different from that encountered in the majority of infectious diseases that scientists have had to develop innovative and diverse approaches to learning how HIV functions and how the body responds to infection with HIV. In most cases of infection, our immune system recognizes that a microorganism has invaded or damaged body cells and quickly destroys the intruder and clears away any damaged cells. In the case of HIV, however, the cellular target of the virus is one part of the immune system itself, called CD4 cells. The unique and complex nature of HIV infection has dictated that researchers first answer some very basic questions about how the virus behaves within the context of the human immune system before they can hope to design therapeutic and protective measures.

Several important basic questions relate to the rate at which HIV reproduces in the body, including how long it takes the body to destroy HIV particles, how long infected immune cells survive, and how quickly the body replaces damaged immune cells. Researchers hope that the answers to these questions may provide important clues about the optimal timing for administering therapeutics.

Researchers have learned that HIV particles and infected cells are destroyed by the immune system after only a few days. Before this happens, however, some of the virus particles reproduce and, in turn, infect new CD4 cells. Thus, HIV-1 replication, CD4 cell infection, and destruction of virus particles and infected cells occurs continuously. Even though the immune system replaces its damaged CD4 cells almost as quickly as it destroys them, it slowly loses ground to the virus with time. Studies also demonstrated that the continuous production of virus particles results in the emergence of drug resistance within a few weeks of treatment. This is because the more times the virus reproduces, the higher the chance that mutations will occur, some of which will cause the virus to be drug resistant. These observations suggest that treatment strategies should be initiated as early in the infection course as possible, when the immune system is still waging a strong fight. However, more research is needed to better understand the processes by which cells are infected and destroyed in order to determine how HIV causes disease and to develop strategies to control and prevent HIV infection and AIDS.

One of the strengths of the NIH system of investigator-initiated research is the multifaceted and simultaneous approach to a problem. In the AIDS arena, for example, some scientists have taken a very different approach from that described above. They focused on a special sub-population of individuals infected with HIV — those who have remained symptom-free for more than 10 years and have healthy immune systems — and asked what sets them apart from the majority of

HIV positive individuals. It is quite likely that no single factor will explain how all such individuals control their HIV infection. For example, intramural researchers discovered that one long-term survivor appears to have been infected with a weakened form of HIV. Although viruses are not living organisms, they nevertheless contain genetic material which produces proteins that allow the virus particles to replicate inside host cells. In this particular case, scientists found that the "weakened" HIV virus was missing a portion of a gene called *nef*. This omission may account for the absence of disease progression in some long-term survivors. It also provides further justification for using a live, genetically weakened strain of the HIV-1 virus as a potential vaccine and suggests new areas of study on immunity to HIV-1 and progression to AIDS.

Still other investigators are focusing on the body's natural defenses against HIV. Researchers have known for almost a decade that certain immune cells in newly infected persons and long-term survivors produce proteins that can suppress HIV replication. After years of searching, NIH scientists believe that they have found three of these proteins. The molecules appear to work together to inhibit the replication of a wide variety of HIV-1, HIV-2 and SIV (monkey AIDS virus) strains in the test tube. The identification of these suppressor proteins opens the door to better understanding of how the immune system fights off HIV in early stages of infection or in long-term survivors. Researchers are continuing to search for additional suppressor molecules produced by the immune cells. These proteins may eventually prove useful as new treatments for AIDS.

Many therapeutic approaches to HIV infection have been thwarted by the fact that the virus rapidly develops drug resistance. Scientists trying to solve this problem recently developed a method for determining the structure of certain key HIV-1 enzymes while they are bound to an inhibitor drug. This allows investigators to visualize how different inhibitor drugs, such as protease inhibitors, physically interact with the viral enzymes. Enzymes are specialized proteins that regulate the rates of chemical reactions in cells. Although viruses are not living cells, they contain enzymes which allow them to invade cells and to reproduce once they are inside cells. The information gained from these studies has opened the door to understanding how to more effectively inhibit enzymes needed for HIV to reproduce and infect cells. This work has made possible the design of anti-HIV drugs. Several potent new anti-viral drugs were discovered as a result of this technology and are now being tested for clinical use. The hope is that these new drugs will remain effective for longer periods and will be able to inhibit HIV that is resistant to existing drugs.

Research aimed at explicating, treating, and preventing AIDS continues to yield information that is proving to be applicable to many other diseases. As the urgency of the AIDS epidemic has given added impetus, for example, to basic immunologic research, a surge of new information is advancing our understanding not only of AIDS, but also of cancer and autoimmune diseases such as systemic lupus erythematosus, type 1 diabetes mellitus, rheumatoid arthritis, and multiple sclerosis. Research on the AIDS virus, HIV, has shed light on the means by which infectious agents and inflammatory cells access the brain; this information has direct implications for studies of Alzheimer's disease, various neuropsychiatric disorders, encephalitis, and meningitis.

Similarly, research on HIV-related wasting is providing valuable scientific and clinical insights into nutritional disorders, metabolic abnormalities, and gastrointestinal dysfunctions.

Research Tools

Many of today's medical treatments would not be possible without the sophisticated research tools and instruments needed for the laboratory studies that underpin most clinical advances. NIH's National Library of Medicine retains its historical leadership role in the introduction and use of computer-based technologies in medical research education and communications, as exemplified in *The Visible Human Project*.

A 59-year old female heart-attack victim and a 39-year old male executed for murder donated their bodies to science. They became the world's first digitized humans when NIH scientists working on the Visible Human Project compiled detailed images of their bodies into a computer database of human anatomy. The process involved, first, embedding the bodies in a special gelatin, which was then frozen to -160°F . After NIH-funded scientists at the University of Colorado obtained CT (computed tomography) and MR (magnetic resonance) images of the bodies, very thin (1 mm) crosswise sections were cut and photographed at high resolution. These images were compiled into complete, anatomically detailed, three-dimensional representations of the bodies. Anyone with access to the Internet can view samples of the Visible Human images. The entire Visible Human Data Set can be readily licensed from NIH's National Library of Medicine. To date, more than 350 license agreements have been signed with 23 countries. The next step in the project — attaching descriptive labels to the visual images — requires computer technologies that do not yet exist; development of the needed linkage programs is now underway at NIH. The aim is to make the NIH's print and image libraries a single, unified resource. Future applications of the Visible Humans will include multi-media "textbooks" for K-12 health education; home health information; college and medical school anatomy courses; planning of surgical and radiation treatments; surgical and endoscopic simulations; a tool for teaching clinical diagnosis; and the development of new medical visualization techniques.

COMMUNICATING THE RESULTS OF MEDICAL RESEARCH WITH THE PUBLIC

The NIH has a longstanding tradition of providing a steady flow of information about important research discoveries, new therapies, and actions individuals can and must take to protect and enhance their own health. When health and well-being are at stake, there is an immediacy and urgency to the information being conveyed. By working with the media, directly responding to inquiries from the public, and communicating with health care professionals, NIH provides the public with the latest information about health and new strategies for the treatment and prevention of disease. For example, NIH is an invaluable resource to the nearly 2 million people who directly request information annually. NIH's *Cancer Information Service* alone has handled more than 6.5 million calls since 1976. In the "Internet Age," increasing the public's access to health care information includes the creation of the *NIH Home Page* on the World Wide Web. NIH is also preparing to put 110 of its "best selling" consumer health booklets on line to increase their accessibility to the general public.

NIH is continually exploring new ways to reach the public. Most recently, NIH funded two pilot episodes on *Health Week*, a Maryland Public Television news magazine about health issues. Topics covered included spinal cord injury, angiogenesis in cancer and heart disease, melatonin and the obesity gene. Story ideas and research materials were supplied by NIH. A unique aspect of the show was the "access points" — phone numbers, Internet addresses and mailing addresses — that provided avenues for further exploration of the health issues covered.

In addition to providing information directly to the general public, NIH communicates medically significant findings to health care professionals in an effort to improve medical practice. One of the primary mandates of the National Library of Medicine is to ensure that the health professions have access to the latest published knowledge. Last year, users of MEDLINE, a database with 8 million references and abstracts to medical journal articles (updated weekly), conducted 7.5 million searches. Half of these searches were for purposes of patient care and were conducted in hospitals, clinics and the offices of individual health care providers around the country. This vital information base connects health care professionals in even the most rural areas of the country to the latest medical and cutting-edge research advances. MEDLINE is by far the most-consulted medical information database in the world.

Another way in which the NIH communicates the results of medical research is through clinical alerts. These provide health-care practitioners with immediate news of significant research advances that impact clinical care. The full range of electronic and print media are utilized in these instances to ensure immediate attention to the life-saving potential of the newest research findings.

Together, these communication efforts help to ensure that the public has access to the most up-to-date, accurate and understandable health information possible.

ECONOMIC BENEFITS OF RESEARCH

Range of Economic Benefits Attributed to NIH-supported Research:

- *NIH research helps support skilled jobs both in NIH-supported laboratories and in the many U.S. companies that provide materials and instruments used in research.*
- *Successes in the biotechnology and pharmaceutical industries are related to NIH support of clinical and especially laboratory research. In 1994, the 1,311 U.S. biotechnology firms employed 103,000 people and generated \$11.2 billion in revenues.*
- *The top 15 U.S. pharmaceutical industries employed more than 350,000 people and earned profits of \$13.3 billion on sales of \$84.8 billion.*
- *NIH support contributes to the vitality of academic institutions that compete for funding. Recent research suggests a direct linkage between the presence of highly productive scientists, most of whom receive NIH support, and an increase in start-ups and the growth of new biotechnology companies.*

As the Nation strives to chart an increasingly sound economic future, every public dollar expended is being scrutinized, and proof of yield on those dollars is demanded. Furthermore, in

the current era, concerns about the costs of and the rise in national medical care expenditures are playing into an intensifying national debate over health care costs. NIH must be part of the solution.

In late 1995, NIH convened an Economics Roundtable on Biomedical Research to help plan how best to measure and articulate the economic benefits of NIH-sponsored research. Three major topics of the discussion included the following:

Defining Biomedical Research Benefits — Any deliberations about the benefits of medical research must take into consideration, and devise more sophisticated approaches capable of measuring the contributions of research to “quality of life.” Innovative economic approaches are also needed to reflect the fact that NIH-sponsored research often leads to clinical interventions which, though neither patentable nor “marketable,” constitute cost-effective measures which substantially improve public health (e.g., studies demonstrating exercise training in late life prevents hip-fracture and subsequent need for institutionalization; research delineating cost-effective community interventions for patients with schizophrenia which significantly limit hospitalization).

Tracking Biomedical Research Impact — As collaboration increases among various players, the economic benefits of basic and clinical NIH-supported research increasingly produce “spill-over” effects on diverse sectors of the American economy. NIH research not only helps to induce a demand for, and creates, skilled jobs in U.S. industries that provide the materials and instruments used in research, but it plays a central role in maintaining the vitality and scientific infrastructure of academic research institutions.

Knowledge generated by NIH-supported research contributes to the success of America’s most successful business and technological enterprises. In addition to its well known contributions to the pharmaceutical and biotechnology industries, NIH-supported research has significantly influenced: agriculture (genetically altered plants and animals are improving yields and extending the shelf life of common foods); manufacturing (genetically-engineered enzymes are revolutionizing the production of many chemicals); and the environmental sciences (modified bacteria and biophysical methods are inexpensively restoring soil and water to their natural states following industrial contamination).

Linking Biomedical Research to Applications in Medical Practice — Economic evaluation of the benefits of medical research can more easily be assessed when findings are evaluated on clinical trials. However, it is still difficult to estimate cost savings and to track the implementation of individual research advances by physicians and health care organizations across the Nation. First, it is difficult to determine the number of patients who could benefit from a new treatment approach. Secondly, less than 100 percent of patients who could benefit from a new treatment will use it, either because they do not have access to the health care system, or because they elect not to see a health care provider. Thirdly, not all physicians will prescribe the latest treatment; and finally, some patients will not comply with their physician’s recommendations. Consequently, the cost-savings examples below represent conservative estimates of the savings that could be achieved were the advances widely implemented. The

projected savings would be even greater if the advance were implemented by all physicians and applied to all patients who have a particular disease or condition.

Economic studies will increasingly be called upon to demonstrate how the federal funds received by NIH significantly improve public health, enhance the productivity of health-related industries, and contribute more generally to the well-being of society and the nation. Often, private firms use the results of research to develop new products, creating jobs and contributing to international competitiveness. In some cases, medical research does not yield marketable products, but still contributes to public health. For example, NIH-funded research has demonstrated that weight training for the frail elderly reduces the risk of falls and the associated costs of hospitalization. By helping to create and sustain a healthy, productive population, NIH provides immeasurable benefits to the nation. With the advice from the Roundtable and other expert groups, the NIH is working to develop improved analytical approaches to assess the range of benefits stemming from medical research.

Examples of Cost-Savings:

- Development of laser-based photocoagulation treatment for early stage diabetic retinopathy can arrest impairment of vision and even blindness at a later stage: \$1.18 - \$1.58 billion per year¹.
- Development of an improved vaccine for the prevention of *Haemophilus influenza* type b (Hib) disease in children 2 month to 5 years of age. Hib is the leading cause of bacterial meningitis in the United States. Prevention of meningitis also protects children from a variety of neurological sequelae, including hearing loss, impairment of vision, mental retardation and seizure disorders: more than \$400 million per year².
- Development of new therapy to cure and prevent the recurrence of peptic ulcer: \$760 million per year³.
- Development of cisplatin in combination therapy for treatment of advanced stage testicular cancer significantly increases the survival rate and, thereby, reduces lifetime work days lost due to premature mortality and morbidity: \$134.0 - \$178.7 million per year⁴.
- Use of hydroxyurea reduces the number of painful crises and the need for chronic transfusion therapy for patients with sickle cell anemia: \$350 million per year⁵.
- Use of clozapine as maintenance treatment for schizophrenia reduces the need for hospitalization: \$1.4 billion per year⁶.
- Use of estrogen replacement therapy reduces the risk of hip fractures in older women and lowers the rate of hip fractures among women aged 65 and older who are taking estrogen: \$333 million per year⁷.

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⁵S. Charache, M. Terrin, R. Moore, et al., "Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia," New England Journal of Medicine, 332: 1317-1322, 1995.

⁶Meltzer et al., American Journal of Psychiatry, 150: 1630-1638, 1993.

⁷William R. Sanslone and Susan P. Stark, "Estrogen Therapy and Fractures: Economic Benefits," Arthritis & Rheumatism, Vol. 38: S342, 1995.

ADMINISTERING NIH

The Warren G. Magnuson Clinical Center

Basic science and clinical medicine converge, each amplifying the other, within the walls of the NIH Clinical Center. Here, patient volunteers from around the Nation, and, occasionally, the world work closely and often heroically with laboratory scientists, clinical investigators, and a dedicated team of nurses and other front-line health care personnel to expand the frontiers of our knowledge about illness and the fundamental processes of life. Over the course of some 40 years, such teamwork has pioneered new treatments for illnesses including depression, certain cancers, AIDS and AIDS-related problems, immunodeficiencies, and sickle cell anemia, to name but a few. The Clinical Center houses nearly half of all federally-funded clinical research beds in the country — and accounts for one-fourth of all federally-funded outpatient, or ambulatory, clinical research visits. Currently, an average of 20,000 children and adults are referred annually to the Clinical Center for experimental treatment and study. These patients account for approximately 65,000 inpatient days and 70,000 outpatient visits for frequently occurring, as well as rare or "orphan," diseases with equal vigor and sophistication.

The Clinical Center is, on several counts, an indispensable national resource. First, from the perspective of medical science, the Center benefits from an unparalleled breadth and depth of expertise; the vast human resources of the surrounding NIH campus afford a critical mass of intellectual energy that is singularly focused on the medical challenges encountered within the Center's walls. Second, the Clinical Center remains one of the premier research training sites in the world. Building on its distinguished record in research "mentoring," the Clinical Center recently launched a formal research training initiative; under it, the more than 100 clinical associates who each year enter 3- to 5-year fellowship programs at the Center will receive systematic training in the array of ethical, legal, scientific, regulatory, and biostatistical issues that today must be mastered by every clinical investigator. Third, from a perspective of health care economics, the Center is one of the few settings in the world where treatment-based research programs remain relatively immune to current health care market-place dictates that assign first priority to cost savings at the expense of developing new knowledge to fight diseases. Changes nationally in the health care financing system are having a dramatic impact upon Academic Medical Centers. Consequently, academic health centers and other research settings are paring back their clinical research programs, limiting both the opportunities for research patients and the types of illnesses under study^{1,2}.

For the reasons enumerated above, it is clear that over the next decade, NIH's intramural clinical research program will be called on to play an increasingly important role in guiding the course of

¹John E. Billi, et al., "Potential Effects of Managed Care on Speciality Practice at a University Medical Center," *The New England Journal of Medicine*, vol. 333, no. 15 (October 12, 1995).

²Robert Mechanic, Allen Dobson, Sylvia Yu, and Lewin-VHI, Inc., "The Impacted of Managed Care on Clinical Research: A Preliminary Investigation," Public Health Service, Contract No. 282-92-0041, Delivery Order 10 (January 1996).

clinical research nationally. Yet, if it is to respond to this urgent national need, the NIH must address the failing infrastructure of the existing 40-year old Center, much of which even now is functionally obsolete, inefficient to operate, and expensive to maintain. The FY 1997 budget requests a total of \$ 310 million to construct a replacement 250-bed hospital and associated laboratories. Facilities in the new Clinical Research Center will be available to physician-scientists in academic health centers as well as to intramural scientists, thus better enabling both intramural NIH and the Nation's overall medical research enterprise broadly to move with renewed vigor into the 21st century.

Reinventing the Clinical Center — In accord with the spirit and aims of the Administration's National Performance Review, the Secretary of HHS last year charged an executive committee of medical scientists and managers to examine the cost-effectiveness and efficiency of Clinical Center operations, and to recommend means of enhancing these measures. Based on a comparative analysis of the Center and thirty academic health centers and other public facilities throughout the country, the Secretary's "Options Team" recommended the following:

- Redesign the Clinical Center's governance structure by setting up a Board of Governors to oversee and then to delegate authority to the Center's director to make independent administrative decisions and generally ensure more effective operational decision making.
- Ensure that the Clinical Center has stable funding in order to optimize opportunities within the Center for operational and fiscal responsibility.
- Develop a Clinical Center strategic plan that is consistent with NIH's overall mission and planning processes. The Board of Governors will have a major responsibility in developing and overseeing the implementation of the strategic plan.
- Provide the NIH Director and Clinical Center leadership greater flexibility in the process of achieving efficiencies in fiscal management, logistics, procurement, and personnel processes. Also permit the Center to carry over, from fiscal year to year, budgeted funds saved through the attainment of more efficient administrative practices. The FY 1997 President's budget proposes to allow funds allocated to the Clinical Center to be made available for two fiscal years.
- Give the Clinical Center authority to recover third party reimbursements for care provided to Clinical Center patients. The FY 1997 Request for NIH has followed up on this recommendation by requesting authority for the Clinical Center to collect third party payments. \$18 million in third party payments is included in the FY 1997 NIH Program Level request of \$12,424 million.

These and other recommendations have been accepted by the Secretary.

Resource Sharing Among NIH Investigators

Many of the advances in medical research that are leading to ever more effective treatments for illness reflect stunning innovations in sophisticated, but often costly, research technologies that are far beyond the capacity of all but a handful of institutions to purchase, construct, or maintain.

NIH recognizes that ensuring broad access to these and other research resources creates efficiencies that makes the research dollar go farther, while providing critical resources to all scientists. Often, access to the needed tools by the largest possible number of scientists determines the pace of research on many devastating illnesses.

A solution to the problem of expensive technologies and scarce resources exists already, and is being practiced in the form of innovative "shared resource" centers funded by NIH and described here. NIH's National Center for Research Resources funds one shared resource network, built around its Shared Instrumentation Grant Program, that involves some 60 biotechnology centers around the country. At present, more than 7,000 investigators use the network for about 5,000 research projects.

Frederick Biomedical Supercomputer Center — Significant improvements in computer technology during the past several years has radically transformed medical research. Scientists have become more dependent on computational methods to exploit and refine biological research techniques and amass data.

The Frederick Biomedical Supercomputing Center (FBSC) is a scientific resource for the world's medical research community. Intramural and extramural researchers can obtain assistance in the use of the latest medical applications. Currently, more than 600 of the Center's 1,900 registered users are extramural scientists, conducting research out of their home institutions. The Center's roster of users continues to increase by about 30 percent annually.

NIH Clinical Center's PET Facility — The NIH's Positron Emission Tomography facility is one of the largest, most active brain scanning programs in the world. At present, over 60 research projects using PET imagers, involving intra- and extramural scientists associated with eight NIH institutes are underway and include collaborations as the one described below.

In the late 1980s, NIH intramural scientists demonstrated that a new compound, named *cyclofoxy*, was a precise tool for neuroimaging and met safety criteria for use in human subjects. An extramural researcher proposed using cyclofoxy in clinical studies of patients with substance abuse disorders and proposed a collaboration with intramural researchers to ascertain the sensitivity and density of brain receptors for opiate drugs in active and recovered drug addicts. Because NIH is a unique source of expertise on the use and analysis of cyclofoxy, the joint project saved the university from having to invest substantial time and funds in attempting to duplicate the NIH accomplishment.

GenBank at NIH's National Library of Medicine — Often, a first step in research aimed at discovering a newly discovered gene's purpose is to look for similar genes with known functions in other organisms, and then to "backtrack" as a way to understanding the underlying biochemistry and physiology of the new, human gene. An indispensable tool in such comparative analyses are genetic databases, which enable scientists to search for and detect relatedness among genes that span over a billion years of molecular evolution.

GenBank is one of the world's most comprehensive computerized archives of DNA sequence data, containing nearly half a million DNA sequences from 15,000 different organisms. NIH scientists have developed innovative retrieval systems, including access through the Internet. On any given day, more than 25,000 searches are performed from many of the 90,000 sites in academic and industrial research settings. This has significantly reduced the need for costly laboratory experiment and accelerated the pace of gene discovery.

The Jackson Laboratory: Animal and Genetic Resources — NIH is the principal source of support of this private, non-profit national and international research resource. Mouse strains maintained by the Jackson Lab include lines which carry spontaneous gene mutations and lines in which new molecular biological techniques have been used to induce specific gene mutations and other informative chromosome abnormalities. Today, the Bioinformatics Program of Jackson Lab, of which the Mouse Genome Database is a component, is a source of information and animal support services extensively used by basic scientists who are developing models of human disease.

Regional Primate Research Centers — Since their establishment in the 1960s, the Nation's seven Regional Primate Research Centers have emerged as a unique and irreplaceable national scientific resource. Nonhuman primates share about 90 percent of the human genome; thus, they are often a vital link between basic research and clinical applications in human diseases. The Primate Research Centers have contributed to medical science in many ways, including in the areas of infectious diseases (especially AIDS and poliomyelitis), reproductive biology, nutrition, cardiovascular diseases, environmental health, and studies of basic mechanisms of behavior.

Streamlining the NIH: Challenges and Opportunities

The "business" of science at NIH is conducted, in large part, through the mechanisms of grants and contracts that support the work of researchers at universities and other research facilities around the Nation. As competition for NIH funds intensifies, achieving optimal operational efficiencies enables NIH to extract maximum research buying power out of appropriated funds, contributing directly to the productivity of the Nation's medical research enterprise.

Inspired by Vice President Gore's *National Performance Review*, NIH continues to refine and expand diverse "reinvention" activities that are designed to remove unnecessary obstacles to the flow of dollars for science. The growing sophistication and adaptability of the country's electronic data web has offered an obvious and already profitable target for streamlining efforts, and key initiatives are described below. NIH managers realize, moreover, that in an age of instantaneous data transfer, outdated or cumbersome internal processes are a significant rate-limiting factor.

Electronic Submission of Grant Application Materials — In the era of a user-friendly Internet and the new World Wide Web (WWW), the NIH is phasing in powerful new elements of its Electronic Research Administration (ERA) initiative.

In 1996, a pilot project to streamline the exchange of information between the NIH and applicant organizations entails construction of a new client/server database that will be an electronic repository of all information generated during the life cycle of a given grant. Accessible to both the authorized grantee and NIH staff, the system ultimately will be capable of handling every aspect of research management. Elements of the ERA initiative now being pilot tested include:

- **The electronic application:** Under a Department of Energy cooperative agreement, NIH and several defense agencies, along with eight grantee institutions, are testing new Electronic Data Interchange standards that will permit extramural investigators to submit electronically much of the "routine" administrative information required for a standard (RO1) research application. An immediate benefit of this will be to relieve universities of the need to submit large packages of nearly identical information on behalf of multiple applicants. Also, by using the new Electronic Data Interchange standards, commercial vendors will be able to develop grant application software that can create data streams for transmission to NIH without the need for compatible processing systems.

- **Electronic invention reporting:** Thirty institutions now are on-line with EDISON, a computerized system designed solely to receive, store, track, sort, and report information about inventions and patents that have resulted from NIH extramural funding. EDISON employs a Netscape browser interface that allows data to be viewed or modified in real-time. Eventually, researchers will be able to transfer, or upload, data directly, without any manual keying at the Netscape interface. EDISON includes a subsystem that reminds a grantee organization of pending reporting requirements. In testing, EDISON has proved to be so user-friendly that several other Federal agencies are adapting NIH's prototype concept to their specific needs.

- **Research Trainee Reporting:** A WWW Netscape browser is being used in this new application to capture information about trainees appointed under the Institutional National Research Service Awards program. In addition to dispensing with the need for paper archiving of voluminous information, the system will provide immediate information on the composition of a significant portion of the Nation's pool of scientists in training.

- **The NIH Home Page:** For WWW users, whether connecting from a congressional office, a research university, or a high school student's home computer, the NIH address — <http://www.nih.gov> — is evolving into an immense resource. The home page, which connects to home pages for each specific NIH unit, allows one access to scientific and health data and to jump to "linked" external sources of information around the Nation and the world.

Peer Review — In this extraordinarily productive and competitive age of medical research, only one in every four investigators who apply for funding get an NIH grant. In order to assure that the most meritorious applications receive thorough reviews — a time- and labor-intensive task not only for NIH staff, but also for scientists from the extramural community who volunteer to serve as peer reviewers — NIH continues to introduce innovations that accelerate the review process and the provision of feedback to applicants on peer review deliberations. In an effort to enhance in-house efficiencies, NIH has regrouped 85 separate and diverse study sections into 18 scientifically-cohesive Initial Review Groups, each of which comprises between 3 and 8 study sections with expertise in a given field. The new structure enables an over-arching IRG to shift study section members to areas of high demand and to specific applications whose proposed direction of inquiry requires hybrid reviewer expertise. Another innovation being explored is the "Just-in-Time" application, wherein an applicant will not be required to submit a detailed budget

or biographical sketch until it is clear that a proposal is likely to be funded on the basis of its scientific merit. This will result in considerable savings of time and effort in the preparation of grant applications.

National Advisory Councils — Oversight of each NIH component is provided by a Council, made up of scientists and persons with expertise in areas outside of medical science. Councils provide a second-level review of peer review judgement of scientific merit and, further, ensure that projects slated to receive funding appropriately meet criteria of public health need and related considerations. Efforts now being pilot tested to enhance Council functions range from a new mail balloting early-approval system for selected grants, to modifications in the amounts and nature of documentation needed by Council members to carry out grant review.

Competitive Service Centers — The push for greater operational efficiency has led to the establishment of Competitive Service Centers. Under this initiative, an institute with expertise in a particular function makes this service available to other institutes to enable them to purchase expert and efficient services without the need to establish these functions within each institute. A number of decentralized collaborative functions are ongoing such as review of grants, procurement, financial and mainframe computing services. The aim of all these efforts is to ensure that more resources can be invested in research, the primary mission of the NIH.

Administrative Practices — In the face of shrinking administrative resources, the NIH is vigorously exploring several approaches aimed at securing greater operational and administrative efficiencies. Several examples will illustrate the momentum and commitment in this area.

The National Heart, Lung and Blood Institute (NHLBI) reorganized its extramural program operations and the Office of the Director. This involved consolidating 59 program offices or branches and resulted in the reduction of several organizational units and supervisory positions. The National Institute of Allergy and Infectious Diseases (NIAID) consolidated and eliminated a number of offices (e.g., Tropical Medicine and Administrative Management) to save resources and eliminate unnecessary levels of review. The National Cancer Institute (NCI) improved the Institute's management structure by establishing a sharper programmatic focus for all intramural and extramural functions. At the same time, NCI merged five separate branches dealing with intramural and extramural administration into two units, increasing efficiency and reducing operating costs.

To reduce administrative burdens across the NIH, the Office of the Director, NIH, simplified requirements for performance management. Similar simplifications are planned for the SES recruitment process, merit staffing for GS employees, and for approval of recruitment and retention bonuses. The NIH is testing an "exception only" time and attendance reporting system in the National Institute of General Medical Sciences (NIGMS) and the National Center for Human Genome Research (NCHGR), which if adopted more broadly, would save approximately one-half of the time currently required for payroll processing. This initiative, conducted with the assistance of the Department of Health and Human Services, would replace the existing, complex and error-prone system. The Office of the Director, NIH, also redelegated 17 of the most critical personnel authorities. These authorities include pay setting, training, awards and "family

friendly" workplace initiatives. This redelegation to line managers eliminates numerous levels of review and approval.

Priority Setting at the NIH

For NIH, the process of setting strategic priorities entails examining a broad constellation of public health needs, scientific opportunities, Executive and Congressional interests, and other factors that bear on the course of the Nation's investment in medical research. Although the process is not reducible to a simple flow chart or time line, it takes place at several distinct levels and is occurring all of the time. There are two pivotal levels where priorities are set: the Institute and Center (IC) Directors and the Director of NIH, where ultimate responsibility lies for the course of federally-funded medical research.

Institute Planning and Priority Setting — In order to set priorities, the IC Director seeks the advice of a number of individuals, including IC program staff and the scientific and public members of the IC's National Advisory Council. The Director engages in ongoing discussions with extramural grantees, intramural investigators as well as with the Administration, members of Congress and the public in order to prioritize research efforts. Advice is specifically sought on: the urgency, from a public health perspective, of an area of research; the top scientific opportunities; gaps in knowledge which merit special effort; the costs of doing the research assessed against its benefits; economic issues, including the potential effects of the research on quality of life; the scientifically and programmatically appropriate balance between intramural and extramural research; the balance between laboratory research and clinical research; and the selection of mechanisms with which to support research, including regular research grants, program projects, R&D contracts, and centers. The IC Director must also consider the range of costs associated with research management, e.g., staffing (FTEs), buildings and facilities and support services, when allocating resources within the IC. This broad program planning effort culminates in a strategic plan which charts the scientific course of the Institute, over several years.

The IC strategic plan provides, however, only one of the decision points in the determination to fund an individual research project. Final funding is based on: 1) a review of the scientific merit of the proposal; 2) Council recommendations, and 3) the IC's priorities (strategic plan). Strategic priority setting subsumes, but is not synonymous with peer review, a fundamentally straightforward process of scientists judging science. To this scientific critique, a program's National Advisory Council overlays its judgement of the relevance of a proposal to the IC's mission and the responsiveness of a proposal to the burden of the disease(s) that the Council ascertains to fall under an IC's purview. Final funding decisions also take into consideration the opportunity in a scientific field, program continuity, and the degree to which a project may have broad applications.

Office of the Director, NIH — The Director is responsible for providing overall leadership to the ICs. This responsibility entails constant attention to individual IC portfolio management, and to both needs and opportunities for crosscutting efforts. The Director is apprised of each IC's priorities and accomplishments through a well-established system of regular senior staff

meetings, NIH interest groups and briefing sessions with IC Directors. Advice is also sought from special panels of experts convened to advise the Director on "trans-NIH" issues (for example, gene therapy; the NIH investment in clinical research; the role of NIH's intramural research program; and the effectiveness/efficiency of NIH peer review procedures.) At the Director's level, this bottom-up information flow converges with top-down discussions with the Department of Health and Human Services (DHHS) and Congress. Because NIH is committed to input from the public, and since Congress is, first and foremost, representative of the public, this dialogue is particularly important.

The Director also assures cross-Institute priority setting by encouraging and expanding intra-Institute collaborations in both planning and research activities. In few instances is a single Institute the sole supporter of research into the causes and consequences of a given disease or into potential treatment and prevention strategies. When appropriate, an individual IC will act as the lead Institute for research on a particular disease, acting to assure NIH-wide coordination and collaboration. Program offices in the Office of the Director are also responsible for some cross-Institute coordination, including women and minority health, AIDS research, disease prevention and behavioral and social science research. The NIH is strongly committed to an integrated approach to developing and implementing research priorities which reflect and anticipate broad conceptualizations of illness and health.

Beyond the process of advice and consultation, the NIH Director has access to several more concrete approaches to highlight and supplement priority areas of scientific opportunity and public health need. Both the Director's Discretionary Fund, and the Director's authority to transfer up to 1 percent of the total NIH budget are used to jump start particularly exciting or urgent areas of research. Use of these mechanisms typically follows extensive discussions between the NIH Director and the ICs to identify particular research initiatives which reflect NIH-wide priorities.

The Director holds primary responsibility within NIH for formulating the Agency's annual budget on the basis of extensive interactions with the ICs, DHHS, and the OMB. The Director also works closely with IC program Directors in articulating and justifying priorities through the Congressional Appropriations process. This annual activity allows for ongoing clarification, justification and discussion of NIH priorities with members of Congress. Thus, the budget provides an established framework within which priorities are continually identified, reviewed and justified.

Government Performance and Results Act/Strategic Planning

NIH leadership is accountable for ensuring that research supported by the agency anticipates and responds to national health needs, while taking advantage of scientific opportunities and imperatives. The Government Performance and Results Act of 1993 (GPRA) underscores this mandate by requiring that all Federal agencies build strategic planning and evaluation into management and development of their programs, ensuring that program results are communicated to Congress and the public. GPRA requires that an agency predict expected program outcomes in advance, and effectively demonstrate attainment of those outcomes.

In providing stewardship for the Nation's investment in biomedical research, NIH faces unique challenges in attempting to predict annual programmatic outcomes in advance. Because advances in knowledge are typically the result of long term, often serendipitous research paths, many of the most important discoveries have come about as a result of experiments undertaken with a very different purpose in mind, such that the results of particular research investigations are largely unknowable in advance. Because basic research outcomes are often the result of decades of effort, are difficult to predict, and have impacts on different goals and customers, the unique nature of the NIH mission requires a response to GPRA that is more specifically tailored to the agency's goals and culture.

NIH is currently developing a GPRA-related 6 year-cycle strategic and performance plan that manifests the agency's aims to maximize support for basic research, promote the Nation's health, enhance understanding of the biologic basis of disease, and improve prevention and treatment of human disorders. The plan will provide researchers and science administrators with the capacity to chart future years' equipment and personnel expenditures, while at the same time building in the flexibility and available resources to address immediate public health needs and research opportunities.

The assurance of flexibility in any planning system is key, since science works best when a multidisciplinary approach is undertaken to collaboratively address the major health problems faced by our citizens. The NIH leadership systematically identifies research opportunities and management issues common to multiple programs across NIH, while periodic reviews by the Director continuously ascertain the need for, and potential payoff of, targeted additional funding. Whether informal or guided by NIH-wide coordinating office, such frequent interaction serves to strengthen the research enterprise's unified purpose to more rapidly advance scientific productivity.

FY 1997 BUDGET POLICY

The Fiscal Year (FY) 1997 President's Budget Requests a program level of \$12,424 million for NIH, a total increase of \$485 million or 4.1 percent over the FY 1996 Estimate, including receipt of an estimated \$18 million in third party reimbursements for the Clinical Center (CC). In budget authority, the request of \$12,406 provides a total increase of \$467 million or 3.9 percent over the FY 1996 Estimate, including \$310 million to fully fund construction of the Clinical Research Center (CRC). Excluding the \$420 million requested for the CRC and Buildings and Facilities (B&F), the NIH budget authority would increase by \$193.5 million or 1.6 percent over the FY 1996 Estimate. Support for AIDS research will increase by \$24.1 million, or 1.7 percent over the FY 1996 Estimate.

DERIVATION OF NIH FY 1997 REQUEST
(Dollars in Millions)

	<u>Level</u>	<u>Percent Increase over FY 1996 Enacted</u>
1) 1996 Enacted Level	\$11,939	
2) Increase for NIH Research	+193	1.6 %
3) Increase for B&F, including CRC	+274	187.4 %
4) Recoveries from third party payments for CC	+ 18	---
Total Program Level	12,424	4.1 %
5) Recoveries from third-party payments for CC	- 18	--
Total Budget Authority	12,406	3.9 %

Basic Goals and Budget Strategy

In developing the FY 1997 President's Budget, NIH has identified goals and a budget strategy to maximize support for basic biomedical research, to promote health and to better understand the biological and behavioral basis for disease to improve prevention and treatment of human disorders. To take advantage of the most promising areas of research, NIH has identified the following areas of scientific emphasis for increase in the Fiscal Year 1997 Budget:

The Biology of Brain Disorders encompasses the basic biology and chemistry and anatomy of the brain, including the physiology of the neuron, its receptors and the neurotransmitters which are responsible for relaying messages between cells. This arena of research extends to studies which seek to understand the development of the normal brain and the changes in development which may underlie brain disorders. This research employs animal models, neuroimaging, and clinical studies in an effort to understand many disorders, such as pain, addiction, mental illness, neurodegenerative disease, diseases of the aging brain, such as Alzheimers, and damage to the sensory system to name but a few. (+ \$22.0 million)

New Approaches to Pathogenesis encompasses studies which seek to determine the pathological consequences of disorders of the normal cell cycle and cell death, as well as the mechanisms of cell and tissue injury which occur as a result of infection, metabolic abnormalities, genetic deficiencies or environmental toxins. Bone and connective tissue disease, autoimmune disorders, virus-cell interactions in AIDs, and cardiomyopathy are but a few examples of research that seek to define mechanisms of pathogenesis. (+ \$20.5 million)

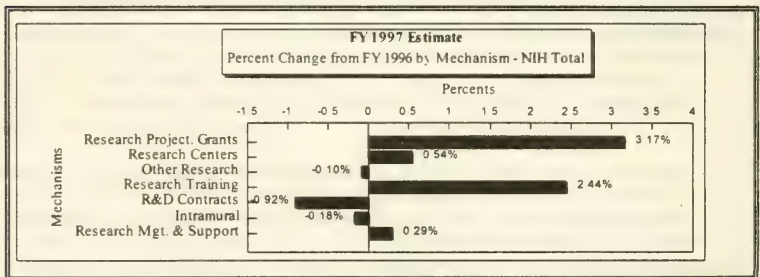
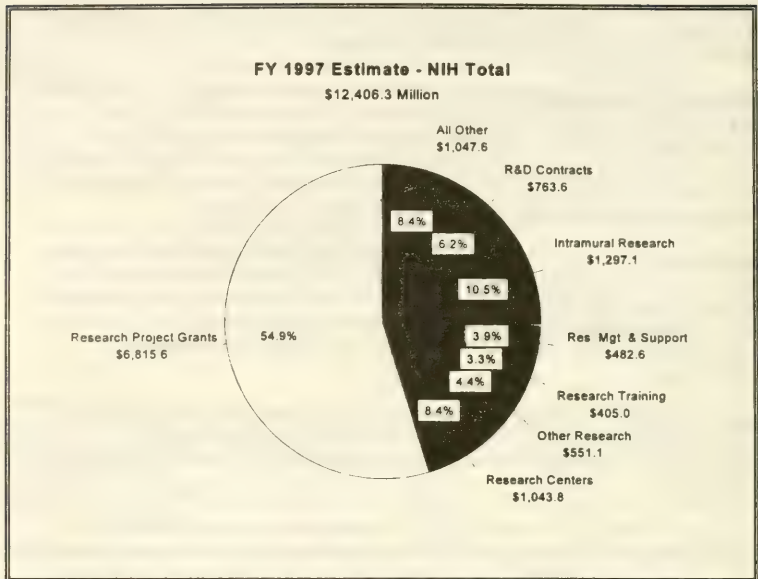
New Preventive Strategies Against Disease involve investigations of emerging infections, as well as the prevention and treatment of drug and alcohol abuse. Vaccines against cancer and infectious diseases such as HIV, otitis media and herpes are included under this category. Prevention also involves the behavioral, genetic and environmental aspects of risk assessment. Also, bionutrition, including the genetic basis of eating disorders and pathological consequences of diet, have become important areas for study in prevention. (+ \$22.5 million)

Genetic Medicine encompasses the analysis of the genome. This research utilizes EST mapping, which involves using expressed sequence tags as chromosomal markers, various methods for sequencing the genome and other technologies. Extensions of these studies include gene therapy initiatives, which incorporate investigations of new target organs and diseases, stem cell biology and vector design. It also includes analysis of complex traits and genetic risk assessment. (+ \$21.0 million)

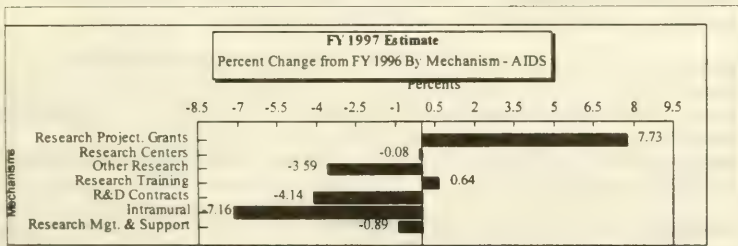
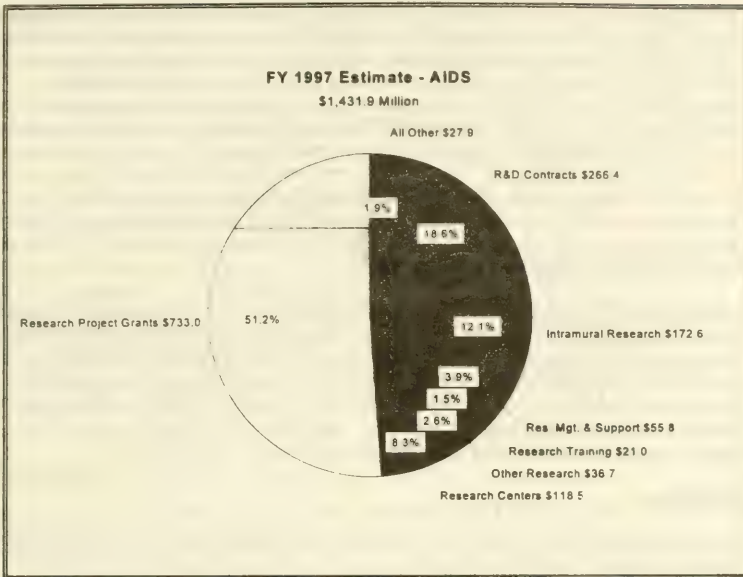
Advanced Instrumentation and Computers in Medicine and Research include novel imaging technologies for diagnosis, therapy, and for the study of cell and structural biology. Telemedicine and shared instrumentation programs are important components of this category. (+ \$13.0 million)

Further, the FY 1997 Request for NIH once again requests that Congress appropriate all NIH AIDS research funds to the NIH Office of AIDS research (OAR). A separate appropriation is the most appropriate vehicle for making decisions about allocation of AIDS research funding and helps target NIH research dollars effectively across all the Institutes and Centers that carry out HIV/AIDS research.

FY 1997 BUDGET OVERVIEW



FY 1997 BUDGET OVERVIEW - AIDS



Mechanism Discussion

NIH's highest priority is the funding of basic biomedical research through research project grants (RPGs). The emphasis on RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. In FY 1997, NIH will support 6,827 competing RPGs, an increase of 207 competing RPGs over the FY 1996 Estimate. Support for RPGs will increase by 2.6 percent over the FY 1996 Estimate; including Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) awards, RPG support will increase by 3.2 percent over the FY 1996 Estimate.

Replacing the Clinical Center's hospital and associated laboratories with the new Clinical Research Center (CRC) is another top priority, for which the FY 1997 budget requests \$310 million to fully fund the construction. Including the \$23 million appropriated in FY 1996 brings the total cost of the CRC project to \$333 million.

NIH continues to be a leader in the training of biomedical and behavioral researchers. Through National Research Service Awards (NRSA), NIH provides the biomedical research enterprise with a steady flow of highly-trained researchers equipped to conduct the Nation's research mission and to strengthen national science literacy and information dissemination programs in the twenty-first century. In the FY 1997 Request, NIH will support 14,749 pre- and postdoctoral trainees in full-time training positions and provide an across-the-board stipend increase of 2.2 percent over the FY 1996 Estimate level, the first stipend increase since FY 1994.

Other Issues

NIH will provide funding in the FY 1997 Request for the National Foundation for Biomedical Research (NFBR). The NFBR is authorized to support and encourage teachers and students of science at all levels of education, and to provide support for biomedical research not possible through current appropriations. In FY 1997, NIH requests up to \$200,000 to establish this foundation. Additional support will come from private donations.

Within the FY 1997 Request, NIH will provide funding for the National Bioethics Advisory Council (NBAC). The NBAC will consider issues of bioethics arising from research on human biology and behavior, and the applications of that research. The Commission will provide advice and make recommendations to the National Science and Technology Council, and other appropriate entities and the public on such bioethical issues. The FY 1997 Request includes up to \$500,000 to support the NBAC.

NIH supports the Administration's commitment to safe passages for children through basic research to improve the physical and mental health and well-being of children.

NIH continues to utilize reinvention and reengineering laboratories and initiatives in the administration of NIH programs both to achieve greater efficiency and to optimize the Nation's investment in biomedical research.

Cost Management

Another top priority for NIH in the FY 1997 Request was to increase the number of competing RPGs by at least 200 awards over the FY 1996 Estimate. NIH has constructed the budget so as to minimize the impact on extramural research of the extraordinary one-year cost of constructing the CRC. To achieve this goal, and consistent with declining inflation indices, rates identified for increases associated with RPGs in *A Plan for Managing the Costs of Biomedical Research*, referred to as the NIH Financial Management Plan (FMP), have been modified. Since FY 1997 inflation rates are projected to decline to 2.2 percent for the Gross Domestic Product (GDP) and 3.7 percent for the Biomedical Research and Development Price Index (BRDPI), noncompeting RPGs would receive direct cost increases of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent.

The apparently flat increase in average costs for competing RPGs including AIDS from FY 1996 to FY 1997 is misleading. The cycling of the unusually expensive AIDS Adult Clinical Trial Groups (ACTGS) from competing to noncompeting status in FY 1997 and the cycling of the much smaller cohort of AIDS Pediatric Clinical Trial Groups from noncompeting to competing status in FY 1997 distort the average cost calculation for competing RPGs. Adjustment to exclude the impact of these two cohorts of AIDS clinical trial result in an average cost increase for competing RPGs of approximately 2 percent in total from FY 1996 to FY 1997.

FULL-TIME EQUIVALENTS

NIH full-time equivalent (FTE) levels have remained constant from FY 1995 to the FY 1997 Request.

FY 1995	FY 1996	FY 1997	CHANGE
15,474	15,474	15,474	0

CONCLUSION

For more than five decades, medical science supported by NIH has benefitted from the unwavering support of our Nation's citizens and their elected leaders. The resolve to create and sustain a program of superlative medical research has yielded multiple benefits, including vast improvements in human health and well-being; significant contributions to the economy; and an extraordinary enrichment of knowledge regarding basic biologic mechanisms, the causes and course of disease, and innovative treatments. The volume of new cutting-edge knowledge generated by NIH-supported investigators engenders a renewed sense of respect for the fragility of human life, underscoring the continuing urgency of the NIH mission.

As illustrated in these pages, the pace of progress in medical science is astoundingly rapid. But it is clear that the most challenging and critical scientific discoveries still lie ahead. Continuing progress entirely depends upon the consistency and generosity of Federal support for medical research.

DHHS - National Institutes of Health

**Summary of Increases for
Non-AIDS Special Emphasis Areas**
(Dollars in thousands)

	FY 1995 Actual	FY 1996 Estimate	FY 1997 ICD/Program Increases	FY 1997 Director's Increases	FY 1997 Estimate
Biology of Brain Disorders	\$2,160,682	\$2,268,852	\$30,641	\$22,000	\$2,321,493
Pathogenesis	1,307,871	1,362,477	19,957	20,500	1,402,934
Preventive Strategies	1,665,185	1,858,641	20,058	22,500	1,901,199
Genetics of Medicine	758,587	801,704	15,748	21,000	838,452
Advanced Instrumentation	231,783	261,753	1,770	13,000	276,523
TOTAL	6,124,108	6,553,427	88,174	99,000	6,740,601

DHHS - NATIONAL INSTITUTES OF HEALTH

Summary of AppropriationsIncludes AIDS

	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
NCI	\$2,130,902,000	\$2,251,084,000	\$2,280,931,000
NHLBI	1,298,059,000	1,355,866,000	1,378,670,000
NIDR	174,845,000	183,196,000	186,781,000
NIDDK	735,726,000	771,252,000	784,923,000
NINDS	650,988,000	681,534,000	695,098,000
NIAD	1,094,706,000	1,169,628,000	1,208,730,000
NIGMS	904,897,000	946,971,000	963,623,000
NICHD	567,698,000	595,162,000	603,650,000
NEI	300,070,000	314,185,000	319,207,000
NIEHS	272,082,000	288,898,000	295,142,000
NIH	433,879,000	453,917,000	463,365,000
NIAMS	232,001,000	242,828,000	247,141,000
NIDCD	168,690,000	176,502,000	180,816,000
NIMH	629,921,000	661,293,000	671,205,000
NIDA	436,928,000	458,441,000	466,325,000
NIAAA	189,805,000	198,607,000	202,614,000
NINR	52,700,000	55,831,000	56,966,000
NCRR	351,971,000	390,339,000	377,599,000
NCHGR	153,899,000	170,041,000	179,875,000
FIC	23,758,000	25,348,000	25,547,000
NLM	127,889,000	141,439,000	146,579,000
OD	238,628,000	260,488,000	251,513,000
SUBTOTAL	11,170,042,000	11,792,850,000	11,986,300,000
B&F	114,120,000	146,151,000	420,000,000
Total, Budget Auth.	11,284,162,000	11,939,001,000	12,406,300,000
Third Party Payments	0	0	18,000,000
Total, Prog. Level	11,284,162,000	11,939,001,000	12,424,300,000

NOTES: Funding for the AIDS portion of the amounts shown above for FY 1995 and FY 1997 are contained in the Office of AIDS Research, NIH.

Third party payments are estimated recoveries for patient care costs to the Clinical Center.

DHHS - NATIONAL INSTITUTES OF HEALTH

Summary of Appropriations
(Dollars in thousands)

	FY 1995 Comparable 1/				FY 1996 Estimate				FY 1997 Estimate 2/				Percent Change 97/96			
	Actual	ICD Estimate	AIDS Distribution	Includes AIDS	ICD Estimate	AIDS Distribution	Includes AIDS		ICD Estimate	AIDS Distribution	Includes AIDS		ICD Estimate	AIDS Distribution	Includes AIDS	
NCI	\$1,913,167	\$2,130,902	\$21,735	\$2,109,167	\$2,025,294	\$275,790	\$2,251,084		\$2,060,392	\$220,539	\$2,280,931		173	-2.33	133	
NHLBI	1,242,574	1,248,059	35,385	1,212,674	1,297,941	57,295	1,355,236		1,320,555	58,115	1,378,670		174	0.33	168	
NIDDK	163,122	173,845	10,732	162,112	170,887	12,309	183,196		174,463	12,318	186,781		209	0.07	196	
NIDK	724,974	735,726	22,751	702,223	759,517	11,735	771,252		777,975	11,948	789,923		177	1.82	177	
NIDM	528,247	557,786	24,539	503,747	657,727	23,807	681,534		671,148	23,960	695,098		204	0.60	199	
NIDM	536,340	564,687	28,347	506,333	673,610	596,018	1,169,628		584,362	624,368	1,208,730		187	4.76	334	
NIDM	580,233	604,897	24,664	555,569	720,836	26,135	746,971		936,573	27,050	963,623		171	3.50	173	
NIDH	291,464	300,070	8,606	282,864	305,060	6,051	311,115		543,441	60,209	603,650		168	-0.83	146	
NEI	298,337	314,879	11,545	286,834	314,185	9,125	323,310		319,207	9,135	328,342		164	0.11	160	
NIH	432,164	433,879	1,715	430,449	453,917	6,051	459,968		461,541	6,028	467,561		222	-0.38	216	
NIA	228,122	233,001	3,675	224,426	238,789	4,039	242,828		243,169	3,972	247,141		208	2.18	208	
NIA	228,122	233,001	3,675	224,426	238,789	4,039	242,828		243,169	3,972	247,141		183	-1.66	178	
NIDCD	467,136	489,921	18,785	448,151	505,110	17,556	522,666		519,489	17,266	536,755		242	4.61	244	
NIH	540,570	569,921	29,351	511,219	567,737	93,556	661,293		578,149	93,066	671,205		183	-0.53	150	
NIDA	288,381	300,070	11,689	276,691	305,110	153,331	458,441		312,014	154,311	466,325		226	0.64	172	
NIDA	180,064	189,805	9,741	170,323	188,472	10,135	198,607		192,280	10,334	202,614		202	1.96	202	
NIDA	46,123	52,700	6,577	40,546	50,935	4,896	55,831		51,951	5,015	56,966		189	2.43	203	
NIDR	287,341	300,070	12,729	274,612	321,969	68,370	390,339		309,344	68,265	377,595		-392	-0.17	-326	
NIDRR	132,836	133,890	6,054	126,782	169,041	1,000	170,041		177,788	9,757	179,547		517	108.70	578	
NIDRR	14,650	15,654	1,004	13,646	15,654	9,634	25,288		15,790	9,757	25,547		0.87	0.65	0.79	
NLM	125,195	127,880	2,684	122,505	138,277	3,162	141,439		143,268	3,311	146,579		3.61	4.71	3.63	
OD	214,234	238,628	24,394	189,834	233,890	26,598	260,488		226,913	24,600	251,513		-2.98	-7.51	-3.45	
Office of AIDS Res.	1,333,875	(1,333,875)	0	0	1,407,824	(1,407,824)	0	0	1,431,908	(1,431,908)	0	0	171	0	0	
Subtotal	11,170,042	0	11,170,042	0	11,792,850	0	11,792,850	0	11,986,300	0	11,986,300	0	164	0	164	
B&F	114,120	0	114,120	0	146,151	0	146,151	0	142,000	0	142,000	0	187.37	0	187.37	
Total, Budget Auth.	11,284,162	0	11,284,162	0	11,939,001	0	11,939,001	0	12,406,300	0	12,406,300	0	3.91	0	3.91	
Third Party Payments, 3/	0	0	0	0	0	0	0	0	18,000	0	18,000	0	4.06	0	4.06	
TOTAL, Prog. Level	11,284,162	0	11,284,162	0	11,939,001	0	11,939,001	0	12,424,300	0	12,424,300	0	4.06	0	4.06	

1/ The funding for HIV/AIDS research is contained in the Office of AIDS Research, NIH. The distribution of this funding is shown by ICD.

2/ The funding for HIV/AIDS research is contained in the Office of AIDS Research, NIH. The distribution of this funding is shown by ICD as a proposed distribution.

3/ Estimated recoveries from third party payments for patient care costs to the Clinical Center.

NATIONAL INSTITUTES OF HEALTH

1997 Congressional Justification

Summary by Mechanism

INCLUDES AIDS

	FY 1995 Budget Authority		FY 1996 Estimate		FY 1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Noncompeting	17069	4,404,044,000	18047	4,733,867,000	18573	4,839,781,000
Admin. supp.	(1,156)	54,667,000	(841)	40,442,000	(914)	40,850,000
Competing	6858	1,587,604,000	6620	1,645,860,000	6827	1,705,387,000
Subtotal, RPGs	23927	6,046,315,000	24667	6,420,169,000	25400	6,586,018,000
SBIR/STTR	1071	173,534,000	1127	186,284,000	1248	229,538,000
Subtotal, RPGs	24998	6,219,849,000	25794	6,606,453,000	26648	6,815,554,000
Research Ctrs:						
Spec/comp	662	738,319,000	655	755,110,000	664	758,021,000
GCRC	78	136,023,000	76	147,495,000	76	148,745,000
Biotech.	62	47,686,000	62	48,542,000	62	49,427,000
CW/BMM	41	57,240,000	41	57,860,000	41	58,470,000
RCMI	17	26,741,000	19	29,106,000	19	29,106,000
Subtotal, Centers	860	1,006,009,000	863	1,038,113,000	862	1,043,769,000
Other Research:						
Careers	2150	187,923,000	2201	200,105,000	2199	201,691,000
Clin. Ed.	67	8,393,000	66	9,412,000	67	9,412,000
Coop. Cl.	412	162,566,000	465	180,378,000	468	179,312,000
BRS	121	17,207,000	190	24,914,000	174	24,104,000
MBRS	100	47,559,000	103	50,562,000	103	50,616,000
Other	563	80,682,000	699	86,326,000	685	86,003,000
Subtotal, Other	3413	504,330,000	3724	551,697,000	3696	551,138,000
Total Res. Grants	29271	7,730,188,000	30381	8,196,263,000	31206	8,410,461,000
Training						
Individual	2556	63,903,000	2459	64,312,000	2474	66,990,000
Institutional	12335	316,643,000	12328	331,031,000	12275	337,965,000
Total Training	14891	380,546,000	14797	395,343,000	14749	404,975,000
R & D Contracts	1186	723,178,000	1272	770,749,000	1236	763,636,000
(SBIR/STTR)	(44)	(9,915,000)	(53)	(11,643,000)	(34)	(8,341,000)
Intramural Research		1,240,674,000		1,299,416,000		1,297,065,000
Res. Mgmt and Support		518,701,000		481,152,000		482,571,000
Cancer Control		192,275,000		225,000,000		227,500,000
Construction		17,963,000		23,000,000		2,000,000
Library of Medicine		127,889,000		141,439,000		146,579,000
Office of the Director		238,628,000		260,488,000		251,513,000
Subtotal		11,170,042,000		11,792,850,000		11,986,300,000
Buildings and Facilities		114,120,000		146,151,000		420,000,000
Total		11,284,162,000		11,939,001,000		12,406,300,000
Clinical Trials		(1,172,633,000)		(1,213,350,000)		(1,224,746,000)

NATIONAL INSTITUTES OF HEALTH

1997 Congressional Justification

Summary by Mechanism

EXCLUDES AIDS

	FY 1995		FY 1996		FY 1997	
	Budget Authority		Estimate		Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Noncompeting	15838	3,957,440,000	16675	4,251,675,000	17163	4,329,404,000
Admin supp.	(1,067)	49,109,000	(794)	36,859,000	(867)	37,202,000
Competing	6364	1,438,266,000	6173	1,467,946,000	6242	1,507,644,000
Subtotal, RPGs	22202	5,444,815,000	22848	5,756,480,000	23405	5,874,250,000
SBIR/STTR	988	160,331,000	1023	169,519,000	1114	208,257,000
Subtotal, RPGs	23190	5,605,146,000	23871	5,925,999,000	24519	6,082,507,000
Research Ctrs:						
Spec/comp	630	692,206,000	634	701,355,000	633	704,461,000
GCRC	78	104,333,000	76	113,834,000	76	115,084,000
Biotech.	82	46,832,000	82	46,688,000	82	47,688,000
CM/BMM	29	34,164,000	30	35,080,000	30	35,480,000
RCMI	17	20,725,000	19	22,599,000	19	22,599,000
Subtotal, Centers	816	898,260,000	821	919,556,000	820	925,312,000
Other Research:						
Careers	2022	176,961,000	2086	188,153,000	2082	189,330,000
Clin. Ed.	67	8,393,000	66	9,412,000	67	9,412,000
Coop. Cl.	408	153,316,000	461	169,744,000	464	170,427,000
BRS	120	16,548,000	190	23,255,000	174	22,445,000
MBRS	100	47,012,000	103	49,977,000	103	50,031,000
Other	523	67,346,000	653	73,104,000	650	72,807,000
Subtotal, Other	3240	469,576,000	3549	513,645,000	3520	514,452,000
Total Res. Grants	27246	6,972,982,000	28241	7,359,200,000	28859	7,522,271,000
Training						
Individual	2469	61,876,000	2383	62,175,000	2387	64,809,000
Institutional	11618	298,540,000	11610	312,334,000	11563	319,199,000
Total Training	14087	360,416,000	13993	374,509,000	13950	384,008,000
R & D Contracts	892	455,199,000	963	492,846,000	943	497,237,000
(SBIR/STTR)	(41)	(8,489,000)	(50)	(11,109,000)	(34)	(8,341,000)
Intramural Research		1,039,757,000		1,113,492,000		1,124,461,000
Res. Mgmt and Support		458,146,000		424,812,000		426,734,000
Cancer Control		192,275,000		225,000,000		227,500,000
Construction		17,963,000		23,000,000		2,000,000
Library of Medicine		125,195,000		138,277,000		143,268,000
Office of the Director		214,234,000		233,890,000		226,913,000
Subtotal		9,836,167,000		10,385,026,000		10,554,392,000
Buildings and Facilities		114,120,000		146,151,000		420,000,000
Total		9,950,287,000		10,531,177,000		10,974,392,000
Clinical Trials		(806,111,000)		(838,435,000)		(851,956,000)

NATIONAL INSTITUTES OF HEALTH

1997 Congressional Justification

Summary by Mechanism

AIDS ONLY

	FY 1995		FY 1996		FY 1997	
	Budget Authority		Estimate		Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Noncompeting	1231	446,604,000	1372	482,192,000	1410	510,377,000
Admin. supp.	(89)	5,558,000	(47)	3,583,000	(47)	3,848,000
Competing	494	149,338,000	447	177,914,000	585	197,743,000
Subtotal, RPGs	1725	601,500,000	1819	663,689,000	1995	711,768,000
SBIR/STTR	83	13,203,000	104	16,765,000	134	21,279,000
Subtotal, RPGs	1808	614,703,000	1923	680,454,000	2129	733,047,000
Research Ctrs:						
Spec/comp	32	46,113,000	31	53,755,000	31	53,560,000
GCRC	0	31,890,000	0	33,661,000	0	33,661,000
Biotech.	0	854,000	0	1,854,000	0	1,739,000
CM/BMM	12	23,076,000	11	22,780,000	11	22,890,000
RCMI	0	6,016,000	0	6,507,000	0	6,507,000
Subtotal, Centers	44	107,749,000	42	118,557,000	42	118,457,000
Other Research:						
Careers	128	10,962,000	135	11,952,000	137	12,361,000
Clin. Ed.	0	0	0	0	0	0
Coop. Cl.	4	9,250,000	4	10,634,000	4	8,885,000
BRS	1	659,000	0	1,659,000	0	1,659,000
MBRS	0	547,000	0	585,000	0	585,000
Other	40	13,336,000	36	13,222,000	35	13,196,000
Subtotal, Other	173	34,754,000	175	38,052,000	176	36,686,000
Total Res. Grants	2025	757,206,000	2140	837,063,000	2347	888,190,000
Training						
Individual	87	2,027,000	86	2,137,000	87	2,181,000
Institutional	717	18,103,000	718	18,697,000	712	18,786,000
Total Training	804	20,130,000	804	20,834,000	799	20,967,000
R & D Contracts	294	267,979,000	309	277,903,000	283	266,399,000
(SBIR/STTR)	(3)	(1,426,000)	(3)	(534,000)	0	0
Intramural Research		200,917,000		185,924,000		172,604,000
Res. Mgmt and Support		60,555,000		56,340,000		55,837,000
Cancer Control		0		0		0
Construction		0		0		0
Library of Medicine		2,694,000		3,162,000		3,311,000
Office of the Director		24,394,000		26,598,000		24,600,000
Subtotal		1,333,875,000		1,407,824,000		1,431,908,000
Buildings and Facilities		0		0		0
Total		1,333,875,000		1,407,824,000		1,431,908,000

Clinical Trials

(366,522,000)

(374,915,000)

(372,790,000)

DHHS - NATIONAL INSTITUTES OF HEALTH
Full-Time Equivalents

ICD	FY 1995 Actual			FY 1996 Estimate			FY 1997 Estimate		
	AIDS	Non-AIDS	Total	AIDS	Non-AIDS	Total	AIDS	Non-AIDS	Total
NCI	280	1,938	2,218	255	1,932	2,187	255	1,932	2,187
NHLBI	12	810	822	12	803	815	12	803	815
NIDR	15	299	314	15	320	335	15	320	335
NIDDK	10	560	570	10	580	590	10	580	590
NINDS	34	615	649	33	609	642	33	609	642
NIAID	361	678	1,039	364	684	1,048	364	684	1,048
NIGMS	2	170	172	2	171	173	2	171	173
NICHD	24	457	481	24	459	483	24	459	483
NEI	8	232	240	8	227	235	8	227	235
NIEHS	9	641	650	10	661	671	10	661	671
NIA	0	426	426	4	416	420	4	416	420
NIAMS	3	144	147	9	149	158	9	149	158
NIDCD	0	125	125	1	133	134	1	133	134
NIMH	38	805	843	34	813	847	34	813	847
NIDA	70	290	360	68	297	365	68	297	365
NIAAA	6	214	220	6	217	223	6	217	223
NINR	6	38	44	6	43	49	6	43	49
NCRR	11	86	97	11	85	96	11	85	96
NCHGR	4	169	173	9	183	192	9	183	192
FIC	4	64	68	4	72	76	4	72	76
Subtotal, ICDs...	897	8,761	9,658	885	8,854	9,739	885	8,854	9,739
NLM	10	565	575	10	561	571	10	561	571
OD	51	681	732	51	606	657	51	606	657
Gen. Svcs....	313	4,079	4,392	307	4,143	4,450	307	4,143	4,450
Undistributed FTEs		4	4		58	58		58	58
Total, NIH....	1,271	14,090	15,361	1,253	14,221	15,474	1,253	14,221	15,474

DHHS—NATIONAL INSTITUTES OF HEALTH

History of Appropriations

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation ^{1/}
1981	\$3,512,320,000	\$3,572,427,000	\$3,564,765,000	\$3,569,406,000 2/
1982	3,310,985,000 3/	3,834,958,000	3,818,710,000	3,641,875,000 4/
1983	3,748,771,000	4,013,450,000	4,028,591,000	4,023,969,000 5/
1984	4,091,958,000	4,314,501,000 6/	4,322,912,000 5/	4,493,588,000 7/
1985	4,566,453,000	4,834,343,000 8/	5,170,203,000	5,149,459,000
1986	4,852,680,000	5,247,836,000 9/	5,463,658,000	5,498,454,000
1986 Sequester				(236,243,000)
1987	4,936,157,000 10/	6,152,775,000	6,080,875,000	6,182,910,000
1988	8,260,277,000 11/	7,036,285,000 12/	6,408,176,000	6,666,693,000
1989	6,535,207,000 13/	6,862,495,000 14/	7,199,298,000	7,152,207,000 14/
1990	6,776,727,000 16/	7,678,625,000 17/	7,713,064,000 17/	7,672,922,000 18/
1990 Sequester				(96,570,000)
1991	7,929,686,000	8,317,654,000 19/	8,347,085,000	8,276,739,000 20/
1991 Sequester				(107,000)
1992	8,774,886,000	8,824,886,000	8,978,133,000	8,921,687,000 21/
1993	10,579,684,000	10,368,551,000	10,387,721,000	10,326,604,000 22/
1994	10,667,984,000	10,936,652,000	10,956,389,000	10,937,653,000 23/
1995	11,473,000,000	11,322,023,000	11,333,181,000	11,299,522,000 24/
1996	11,773,066,000	11,939,001,000	11,639,204,000	11,939,001,000 25/
1997	12,406,300,000 26/			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Authority was a Continuing Resolution; reflects a rescission of \$47,041,000 under P.L. 97-12.

3/ September budget; original request was \$3,762,483,000.

4/ Continuing resolution was the lower of the House or Senate Allowance less a 4% reduction.

5/ Authority was a Continuing Resolution.

6/ Excludes \$166,368,000 not considered.

7/ Includes \$175,838,000 authorized under a Continuing Resolution.

8/ Includes \$237,435,000 for NRSA training, not considered.

9/ Excludes \$217,943,000 for NRSA training, not considered.

10/ Reflects transfer of AIDS research activities to OASH. The House allowance consolidated AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation distributed the funds among the Institutes.

11/ Includes proposed advanced appropriation of \$2,726,000 for outyear cost of competing RPGs in 1988.

12/ The House allowance consolidated AIDS funding in OASH.

13/ The 1989 request excludes funds for AIDS, proposed for consolidation in OASH.

14/ Excludes \$249,464,000 not considered.

15/ Includes real transfer of \$7,443,000 to OASH for AZT.

16/ The 1990 request excludes funds for AIDS, proposed for consolidation in OASH.

17/ Includes \$752,670,000 for AIDS research.

18/ Reflects reductions of \$10,000,000 for extramural salary cap savings, \$4,000,000 for procurement reform and a \$10,428,000 reduction in salaries & expense.

19/ Excludes \$304,814,000 not considered.

20/ Reflects enacted administrative reduction of \$29,909,000 for salaries and expense and \$205,134,000 associated with the 2.41 percent across the board reduction.

21/ Reflects enacted administrative reduction of \$69,603,000 for salaries and expense a travel reduction of \$5,984,000, and a rescission of \$13,131,000.

22/ Reflects enacted administrative reductions of an across the board .8 percent for \$83,571,000, \$34,857,000 for salaries and expenses and a consultant services reduction of \$1,342,000. All columns adjusted to include transfer from ADAMHA.

23/ Reflects a salaries and expense rescission of \$18,120,000. Excludes \$1,000,000 supplemental in NCRR for earthquake relief.

24/ Includes \$1,299,328,000 for HIV Research appropriated to the NIH Office of AIDS Research.

Reflects enacted reductions of \$7,446,000 for procurement, \$345,000 for rent and \$4,401,000 for bonus pay, and rescissions of \$10,000,000 in NCRR for construction and \$12,384,000 in administrative cos

25/ Includes \$1,407,824,000 appropriated to the ICD's for HIV Research.

26/ Includes \$1,431,908,000 for HIV Research in the NIH Office of AIDS Research.

DHHS-National Institutes of Health
HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1986 - 1996
(Dollars in thousands)

FISCAL YEAR	NCI	NHLBI	NIDR	NIDDK	NINDS	NIAD	NIGMS	NICHD	NEI	NIHES	NIA	NIAMS	NIDCD
1986	\$1,203,369	\$822,292	\$98,841	\$544,858	\$414,727	\$366,964	\$492,630	\$307,958	\$186,705	\$188,986	\$149,762		
1987	1,402,837	930,001	117,945	511,124	490,233	545,523	570,916	366,780	216,637	209,294	177,681	\$138,713	
1988	1,469,327	965,536	126,297	534,733	534,682	538,800	532,676	396,811	224,947	215,656	194,746	147,679	
1989	1,570,349	1,045,509	130,709	559,494	472,291	740,257	682,213	425,375	231,170	223,403	222,639	159,891	\$94,166
1990	1,634,332	1,072,354	135,749	581,477	490,409	832,977	681,762	442,914	236,533	229,234	239,455	168,930	117,583
1991	1,714,784	1,126,942	148,918	615,272	541,743	906,251	786,040	478,956	253,241	241,026	323,752	193,247	134,935
1992	1,962,587	1,188,593	158,417	658,925	577,938	959,082	810,814	518,251	268,978	248,575	383,382	203,047	148,789
1993	1,981,351	1,214,793	161,301	681,342	600,078	979,471	832,581	557,788	276,188	251,187	399,924	212,456	154,814
1994	2,082,267	1,277,880	169,520	716,054	630,650	1,065,583	875,511	555,195	290,260	264,249	420,303	223,280	162,823
1995	1,913,819	1,257,374	162,430	726,949	627,045	535,199	876,778	512,165	291,085	268,566	431,991	228,176	166,660
1996	2,251,084	1,355,866	183,196	771,252	681,534	1,169,628	946,971	595,162	314,185	288,898	453,917	241,828	176,502

FISCAL YEAR	NIMH	NIDA	NIAAA	NINR	NCRR	NCHGR	FIC	NLM	OD	B&F	OAR	TOTAL
1986					\$292,523		\$11,054	\$55,322	\$111,961	\$14,259		\$5,202,211
1987				\$20,000	322,860		11,420	61,838	57,208	31,900		6,182,910
1988				23,380	388,153		15,651	67,910	61,819	47,870		6,656,693
1989				29,133	398,076		15,790	73,731	72,076	36,492		7,144,764 1/
1990				33,513	353,734	\$59,538	15,516	81,861	107,419	61,042		8,276,735 2/
1991				38,722	335,255	87,418	17,519	91,408	97,651	168,687		8,921,687 4/
1992				44,929	314,213	104,782	19,593	99,008	141,654	103,840		10,335,996 5/
1993	\$583,851	\$403,806	\$176,619	48,119	312,468	108,239	19,733	113,031	190,325	108,731		10,955,773 6/
1994	613,444	425,201	185,617	51,018	331,915	128,701	21,677	119,981	233,605	111,039		11,299,522 7/
1995	542,200	290,029	181,150	48,164	284,693	151,518	14,646	125,303	217,882	114,120	\$1,333,570	11,939,001 8/
1996	661,326	458,441	198,607	55,831	390,339	170,041	25,313	141,439	261,488	146,151		

NOTE: Includes \$10,000 transferred from "Special Cancer Research" appropriation.

1/ Reflects a 1.2% administrative reduction and procurement reform and transfer to OASH for AZT.

2/ Reflects reductions for Extramural Salary Cap, Procurement Reform, SAE, and Sequestration.

3/ Reflects 2.41% reduction and NIH's share of the \$50M reduction for Salaries and Expenses.

4/ Reflects reductions for travel and Salaries and Expenses.

5/ Reflects an across the board .8 percent reduction and reductions for Salaries and Expenses and Consultant Services.

6/ National Center of Nursing Research elevated to Institute status in 1994.

7/ Reflects enacted reductions of \$7,446 for procurement, \$345 for rent, \$4,401 bonus pay and a rescission of \$20,533.

8/ Funds for HIV Research in the amount of \$1,407,824 appropriated to the ICD's.

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
NIH TOTAL

BUDGET AUTHORITY BY OBJECT

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$449,686,000	\$463,769,000	+\$14,083,000
Other than full-time permanent	98,482,000	102,404,000	+3,922,000
Other personnel compensation	21,439,000	22,020,000	+581,000
Special Personnel Services	83,743,000	87,981,000	+4,238,000
Total, Personnel Compensation	653,350,000	676,174,000	+22,824,000
Personnel Benefits:			
Civilian personnel benefits	136,497,000	140,995,000	+4,498,000
Benefits for former personnel	2,301,000	2,361,000	+60,000
Travel and transportation of persons	18,284,000	18,502,000	+218,000
Transportation of things	3,645,000	3,589,000	-56,000
Rental Payments to GSA	6,723,000	6,896,000	+173,000
Rental payments to others	4,834,000	4,850,000	+16,000
Communications, utilities, and miscellaneous charges	42,317,000	43,420,000	+1,103,000
Printing and reproduction	14,400,000	14,604,000	+204,000
Consulting services	17,960,000	17,880,000	-80,000
Other services	372,675,000	633,946,000	+261,271,000
Purchases from Govt Accts	786,122,000	816,357,000	+30,235,000
Operation & Maintenance of Facili.	71,797,000	71,304,000	-493,000
R&D Contracts	836,463,000	775,707,000	-60,756,000
Medical Care	4,990,000	4,914,000	-76,000
Operation & Maintenance of Equip.	23,658,000	23,504,000	-154,000
Subsistence & Support of Persons	7,111,000	7,162,000	+51,000
Supplies and materials	129,111,000	127,907,000	-1,204,000
Equipment	82,150,000	81,209,000	-941,000
Lands and structures	42,000	42,000	0
Investments & Loans	0	0	0
Grants, subsidies, and contributions	8,722,322,000	8,932,739,000	+210,417,000
Insurance claims and indemnities	2,187,000	2,175,000	-12,000
Interest and dividends	62,000	63,000	+1,000
Refunds	0	0	0
TOTAL OBLIGATIONS	11,939,001,000	12,406,300,000	+467,299,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
AIDS

BUDGET AUTHORITY BY OBJECT

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$42,704,000	\$44,294,000	+\$1,590,000
Other than full-time permanent	8,852,000	9,143,000	+291,000
Other personnel compensation	2,236,000	2,266,000	+30,000
Special Personnel Services	4,220,000	4,347,000	+127,000
Total, Personnel Compensation	58,012,000	60,050,000	+2,038,000
Personnel Benefits:			
Civilian personnel benefits	13,634,000	14,078,000	+444,000
Benefits for former personnel	202,000	210,000	+8,000
Travel and transportation of persons	2,657,000	2,632,000	-25,000
Transportation of things	443,000	428,000	-15,000
Rental Payments to GSA	2,137,000	2,201,000	+64,000
Rental payments to others	875,000	825,000	-50,000
Communications, utilities, and miscellaneous charges	3,501,000	3,516,000	+15,000
Printing and reproduction	1,180,000	1,119,000	-61,000
Consulting services	3,975,000	4,170,000	+195,000
Other services	58,366,000	42,598,000	-15,768,000
Purchases from Govt Accts	107,449,000	106,480,000	-969,000
Operation & Maintenance of Facili.	28,582,000	29,151,000	+569,000
R&D Contracts	235,402,000	221,882,000	-13,520,000
Medical Care	556,000	539,000	-17,000
Operation & Maintenance of Equip.	1,588,000	1,547,000	-41,000
Subsistence & Support of Persons	0	0	0
Supplies and materials	23,903,000	23,838,000	-65,000
Equipment	7,279,000	7,310,000	+31,000
Lands and structures			
Investments & Loans	0	0	0
Grants, subsidies, and contributions	857,897,000	909,157,000	+51,260,000
Insurance claims and indemnities	181,000	172,000	-9,000
Interest and dividends	5,000	5,000	-----
Refunds	0	0	0
TOTAL OBLIGATIONS	1,407,824,000	1,431,908,000	+24,084,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
NON-AIDS

BUDGET AUTHORITY BY OBJECT

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$406,982,000	\$419,475,000	+\$12,493,000
Other than full-time permanent	89,630,000	93,261,000	+3,631,000
Other personnel compensation	19,203,000	19,754,000	+551,000
Special Personnel Services	79,523,000	83,634,000	+4,111,000
Total, Personnel Compensation	595,338,000	616,124,000	+20,786,000
Personnel Benefits:			
Civilian personnel benefits	122,863,000	126,917,000	+4,054,000
Benefits for former personnel	2,099,000	2,151,000	+52,000
Travel and transportation of persons	15,627,000	15,870,000	+243,000
Transportation of things	3,202,000	3,161,000	-41,000
Rental Payments to GSA	4,586,000	4,695,000	+109,000
Rental payments to others	3,959,000	4,025,000	+66,000
Communications, utilities, and miscellaneous charges	38,816,000	39,904,000	+1,088,000
Printing and reproduction	13,220,000	13,485,000	+265,000
Consulting services	13,985,000	13,710,000	-275,000
Other services	314,309,000	591,348,000	+277,039,000
Purchases from Govt Accts	678,673,000	709,877,000	+31,204,000
Operation & Maintenance of Facili	43,215,000	42,153,000	-1,062,000
R&D Contracts	601,061,000	553,825,000	-47,236,000
Medical Care	4,434,000	4,375,000	-59,000
Operation & Maintenance of Equip.	22,070,000	21,957,000	-113,000
Subsistence & Support of Persons	7,111,000	7,162,000	+51,000
Supplies and materials	105,208,000	104,069,000	-1,139,000
Equipment	74,871,000	73,899,000	-972,000
Lands and structures	42,000	42,000	0
Investments & Loans	0	0	0
Grants, subsidies, and contributions	7,864,425,000	8,023,582,000	+159,157,000
Insurance claims and indemnities	2,006,000	2,003,000	-3,000
Interest and dividends	57,000	58,000	+1,000
Refunds	0	0	0
TOTAL OBLIGATIONS	10,531,177,000	10,974,392,000	+443,215,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
BUDGET AUTHORITY BY OBJECT
INCLUDING
SERVICE AND SUPPLY
AND MANAGAEMENT FUND

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	635,172,000	650,608,000	+15,436,000
Other than full-time permanent	111,870,000	115,850,000	+3,980,000
Other personnel compensation	35,385,000	36,031,000	+646,000
Special Personnel Services	85,256,000	89,518,000	+4,262,000
Total, Personnel Compensation	867,683,000	892,007,000	+24,324,000
Personnel Benefits:			
Civilian personnel benefits	182,723,000	187,566,000	+4,843,000
Benefits for former personnel	4,134,000	4,194,000	+60,000
Travel and transportation of persons	18,284,000	18,502,000	+218,000
Transportation of things	3,645,000	3,589,000	-56,000
Rental Payments to GSA	6,723,000	6,896,000	+173,000
Rental payments to others	4,834,000	4,850,000	+16,000
Communications, utilities, and miscellaneous charges	42,317,000	43,420,000	+1,103,000
Printing and reproduction	14,400,000	14,604,000	+204,000
Consulting services	17,960,000	17,880,000	-80,000
Other services	372,675,000	633,946,000	+261,271,000
Purchases from Govt Accts	523,730,000	552,120,000	+28,390,000
Operation & Maintenance of Facili.	71,797,000	71,304,000	-493,000
R&D Contracts	836,463,000	775,707,000	-60,756,000
Medical Care	4,990,000	4,914,000	-76,000
Operation & Maintenance of Equip.	23,658,000	23,504,000	-154,000
Subsistence & Support of Persons	7,111,000	7,162,000	+51,000
Supplies and materials	129,111,000	127,907,000	-1,204,000
Equipment	82,150,000	81,209,000	-941,000
Lands and structures	42,000	42,000	0
Investments & Loans	0	0	0
Grants, subsidies, and contributions	8,722,322,000	8,932,739,000	+210,417,000
Insurance claims and indemnities	2,187,000	2,175,000	-12,000
Interest and dividends	62,000	63,000	+1,000
Refunds	0	0	0
NIH TOTAL OBLIGATIONS	11,939,001,000	12,406,300,000	+467,299,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
NON-AIDS

PERSONNEL COMPENSATION & ADMINISTRATIVE COST

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$406,982,000	\$419,475,000	+\$12,493,000
Other than full-time permanent	89,630,000	93,261,000	+3,631,000
Other personnel compensation	19,203,000	19,754,000	+551,000
Special Personnel Services	79,523,000	83,634,000	+4,111,000
Total, Personnel Compensation	595,338,000	616,124,000	+20,786,000
Personnel Benefits:			
Civilian personnel benefits	122,863,000	126,917,000	+4,054,000
Benefits for former personnel	2,099,000	2,151,000	+52,000
Travel and transportation of persons	15,627,000	15,870,000	+243,000
Transportation of things	3,202,000	3,161,000	-41,000
Rental payments to others	3,959,000	4,025,000	+66,000
Communications, utilities, and miscellaneous charges	38,816,000	39,904,000	+1,088,000
Printing and reproduction	13,220,000	13,485,000	+265,000
Consulting services	12,835,000	12,570,000	-265,000
Other services	167,895,000	171,096,000	+3,201,000
Purchases from Govt Accts	457,685,000	456,032,000	-1,653,000
Operation & Maintenance of Facili.	20,950,000	20,392,000	-558,000
Operation & Maintenance of Equip.	22,851,000	22,738,000	-113,000
Subsistence & Support of Persons	7,104,000	7,155,000	+51,000
Supplies and materials	104,301,000	103,142,000	-1,159,000
TOTAL, NON-AIDS	1,588,745,000	1,614,762,000	+26,017,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
AIDS

PERSONNEL COMPENSATION & ADMINISTRATIVE COST

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$42,704,000	\$44,294,000	+\$1,590,000
Other than full-time permanent	8,852,000	9,143,000	+291,000
Other personnel compensation	2,236,000	2,266,000	+30,000
Special Personnel Services	4,220,000	4,347,000	+127,000
Total, Personnel Compensation	\$8,012,000	60,050,000	+2,038,000
Personnel Benefits:			
Civilian personnel benefits	13,634,000	14,078,000	+444,000
Benefits for former personnel	202,000	210,000	+8,000
Travel and transportation of persons	2,657,000	2,632,000	-25,000
Transportation of things	443,000	428,000	-15,000
Rental payments to others	875,000	825,000	-50,000
Communications, utilities, and miscellaneous charges	3,501,000	3,516,000	+15,000
Printing and reproduction	1,180,000	1,119,000	-61,000
Consulting services	3,977,000	4,172,000	+195,000
Other services	58,364,000	42,593,000	-15,771,000
Purchases from Govt Accts	79,636,000	78,808,000	-828,000
Operation & Maintenance of Facili.	105,000	105,000	0
Operation & Maintenance of Equip.	556,000	539,000	-17,000
Subsistence & Support of Persons	0	0	0
Supplies and materials	23,903,000	23,838,000	-65,000
TOTAL, AIDS	247,045,000	232,913,000	+14,132,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
NIH TOTAL

PERSONNEL COMPENSATION & ADMINISTRATIVE COST

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$449,686,000	\$463,769,000	+\$14,083,000
Other than full-time permanent	98,482,000	102,404,000	+3,922,000
Other personnel compensation	21,439,000	22,020,000	+581,000
Special Personnel Services	83,743,000	87,981,000	+4,238,000
Total, Personnel Compensation	653,350,000	676,174,000	+22,824,000
Personnel Benefits:			
Civilian personnel benefits	136,497,000	140,995,000	+4,498,000
Benefits for former personnel	2,301,000	2,361,000	+60,000
Travel and transportation of persons	18,284,000	18,502,000	+218,000
Transportation of things	3,645,000	3,589,000	-56,000
Rental payments to others	4,834,000	4,850,000	+16,000
Communications, utilities, and miscellaneous charges	42,317,000	43,420,000	+1,103,000
Printing and reproduction	14,400,000	14,604,000	+204,000
Consulting services	16,812,000	16,742,000	-70,000
Other services	226,259,000	213,689,000	-12,570,000
Purchases from Govt Accts	537,321,000	534,840,000	-2,481,000
Operation & Maintenance of Facili	21,055,000	20,497,000	-558,000
Operation & Maintenance of Equip.	23,407,000	23,277,000	-136,000
Subsistence & Support of Persons	7,104,000	7,155,000	+51,000
Supplies and materials	128,204,000	126,980,000	-1,224,000
TOTAL, NIH	1,835,790,000	1,847,675,000	+11,879,000

NATIONAL INSTITUTES OF HEALTH
National Support for Performance of Medical and Health-Related R&D, by Source of Funds
 Fiscal Years 1984 - 1994
 (Dollars in millions)

Source of Funds	FY 1984	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994
TOTAL	\$12,160	\$13,567	\$14,888	\$16,933	\$19,003	\$20,918	\$23,085	\$25,886	\$29,240	\$31,032	\$32,819
Government											
Federal	6,883	7,669	7,923	9,029	9,726	10,629	11,416	12,435	13,660	14,108	14,537
NIH	6,087	6,791	6,895	7,847	8,431	9,163	9,791	10,602	11,726	12,051	12,341
State and Local	(4,257)	(4,828)	(5,005)	(5,852)	(6,292)	(6,778)	(7,136)	(7,696)	(8,407)	(9,763)	(10,328)
	796	878	1,028	1,182	1,295	1,466	1,625	1,833	1,934	2,055	2,196
Industry	4,771	5,360	6,193	7,105	8,438	9,407	10,719	12,361	14,367	15,711	17,106
Private nonprofit											
Foundations	508	538	782	799	839	882	960	1,090	1,183	1,215	1,276
Voluntary health agencies	111	122	129	161	155	129	155	175	213	201	212
Howard Hughes Medical Institute	204	232	260	285	323	354	363	393	421	465	483
Other	79	51	247	183	179	197	215	250	258	251	262
	112	133	146	170	182	202	227	272	291	298	319

NOTES:

1. This table excludes research training and construction.
2. These figures report support for the direct conduct of biomedical research. In addition, HHMI's Office of Grants and Special Programs provides support for scientific career development, which is not included here.

Source: NIH Data Book, 1994

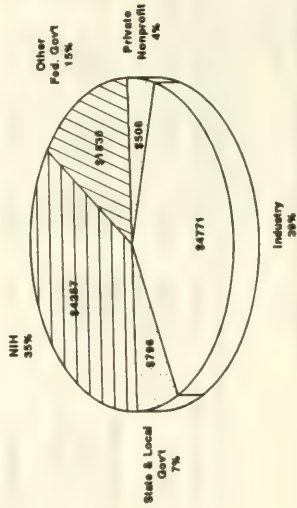
NATIONAL INSTITUTES OF HEALTH Medical and Related R&D

(Dollars in Millions)

FY 1984

Total \$12,160

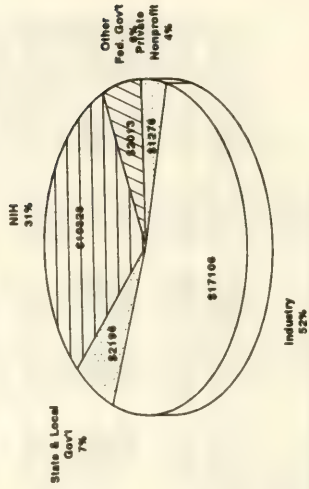
Total Gov't = 57%



FY 1994

Total \$32,919

Total Gov't = 44%



DHHS - NATIONAL INSTITUTES OF HEALTH

STATISTICAL DATA - RESEARCH GRANTS, DIRECT AND INDIRECT COSTS AWARDED 1/
(Dollars in thousands)

Fiscal Year	Direct Costs Awarded	Indirect Costs Awarded	Total Dollars Awarded	Percent To Total In Dollars		Percent Growth In Dollars	
				Direct	Indirect	Direct	Indirect
1982	\$1,610,679	\$689,855	\$2,300,534	70.0	30.0	--	--
1983	1,793,207	791,580	2,584,787	69.4	30.6	11.3	14.7
1984	2,036,639	921,627	2,958,266	68.8	31.2	13.6	16.4
1985	2,343,216	1,069,707	3,412,923	68.7	31.3	15.1	16.1
1986	2,444,946	1,119,115	3,564,061	68.6	31.4	4.3	4.6
1987	2,876,830	1,311,539	4,188,369	68.7	31.3	17.7	17.2
1988	3,124,042	1,416,716	4,540,758	68.8	31.2	8.6	8.0
1989	3,315,563	1,530,547	4,846,110	68.4	31.6	6.1	8.0
1990	3,428,392	1,599,286	5,027,678	68.2	31.8	3.4	4.5
1991	3,748,778	1,744,378	5,493,156	68.2	31.8	9.3	9.1
1992	4,169,928	1,896,215	6,066,143	68.7	31.3	11.2	8.7
1993	4,888,871	2,183,265	7,072,136	69.1	30.9	17.2	15.1
1994	5,098,605	2,279,984	7,378,589	69.1	30.9	4.3	4.4
1995	5,363,762	2,362,067	7,725,829	69.4	30.6	5.2	3.6
1996 Estimate	5,633,793	2,519,309	8,153,102	69.1	30.9	5.0	6.7
1997 Estimate	5,790,033	2,589,175	8,379,208	69.1	30.9	2.8	2.8

Note-- 1992 and prior years data excludes NIMH, NIAAA, and NIDA. Comparable data is not available.

1/ Actual data from the Indirect Cost Management System (ICMS). Includes research project grants, research centers, research career awards, organ systems, clinical education, cooperative clinical research, minority biomedical research support and cancer control grants.

NATIONAL INSTITUTES OF HEALTH
Research Project Grants
Total Number of Awards and Dollars
(Dollars in Thousands)

INCLUDES AIDS

	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Resigned	FY 1995 Bud. Auth.	FY 1996 Estimate	FY 1997 Estimate
No. of Awards:											
Competing	6,867	6,157	5,620	6,462	6,768	6,149	6,822	6,474	6,858	6,620	6,827
Subtotal (includes Noncomp)	22,017	22,725	22,527	23,352	24,033	23,952	24,401	24,050	23,927	24,667	25,400
SBIR								814	1,071	1,127	1,248
Total	22,017	22,725	22,527	23,352	24,033	23,952	24,401	24,864	24,998	25,794	26,648
Average Annual Cost:											
Competing	\$175.2	\$182.3	\$196.7	\$208.1	\$220.3	\$218.3	\$223.3	\$225.0	\$231.5	\$248.6	\$249.8
Subtotal (includes Noncomp)	\$183.0	\$193.9	\$205.3	\$216.1	\$227.2	\$236.2	\$244.1	\$243.5	\$252.7	\$260.3	\$259.3
Percent Change from prior year:											
Competing	4.0%	5.9%	7.9%	5.8%	5.9%	-0.9%	2.3%	3.1%	2.9%	7.4%	0.5%
Total	5.9%	5.9%	5.9%	5.2%	5.1%	4.0%	3.4%	3.1%	3.8%	3.0%	-0.4%
Average Length of Award in Years	4.0	4.1	4.1	3.9	3.9	3.9	3.9	3.8	3.9	3.8	3.9

NOTE: FY 1988 - FY 1994 Comparable number of competing awards includes SBIR/STTR.
FY 1994 Actual - FY 1997 Estimate number of competing awards excludes SBIR/STTR.

NATIONAL INSTITUTES OF HEALTH
Research Project Grants
Success Rates
FY 1988 - FY 1987

INSTITUTE	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Reallocated	FY 1995 Bud. Auth.	FY 1996 Estimate	FY 1997 Estimate
NCI	33%	25%	24%	28%	32%	25%	22%	22%	26%	26%	22%
NHLBI	31%	26%	25%	28%	29%	22%	27%	23%	27%	22%	23%
NIDR	25%	23%	21%	30%	27%	24%	31%	37%	29%	22%	24%
NIDDK	32%	26%	23%	27%	33%	22%	22%	25%	27%	19%	25%
NINDS	40%	32%	24%	30%	27%	25%	22%	26%	31%	23%	23%
NIAID	31%	30%	27%	31%	30%	29%	27%	25%	25%	25%	22%
NIGMS	39%	28%	22%	34%	36%	30%	29%	33%	39%	35%	31%
NICHHD	25%	24%	19%	25%	26%	21%	21%	21%	18%	17%	17%
NEI	43%	43%	38%	33%	31%	32%	31%	40%	36%	35%	39%
NIEHS	29%	26%	28%	28%	28%	21%	21%	26%	15%	22%	25%
NIA	25%	23%	21%	30%	29%	23%	25%	25%	29%	33%	28%
NIAMS	26%	28%	20%	31%	18%	21%	19%	20%	24%	24%	22%
NIDCD	40%	38%	37%	31%	30%	29%	28%	32%	34%	29%	28%
NIMH	29%	29%	24%	27%	27%	20%	27%	21%	19%	17%	18%
NIDA	19%	38%	37%	31%	31%	32%	31%	33%	30%	23%	23%
NIAAA	27%	38%	34%	23%	32%	19%	30%	29%	22%	18%	15%
NINR	27%	19%	16%	19%	15%	11%	11%	12%	32%	21%	27%
NICRR	0%	0%	22%	29%	33%	28%	27%	18%	23%	46%	49%
NCHGR	0%	0%	23%	38%	22%	28%	17%	28%	26%	28%	33%
FIC	0%	0%	0%	0%	0%	0%	6%	27%	65%	32%	28%
NIH	31%	28%	25%	29%	30%	25%	25%	25%	27%	24%	23%

NATIONAL INSTITUTES OF HEALTH

History Of Obligations By Total Mechanism

FY 1988 - FY 1997

(Dollars in Thousands)

INCLUDES AIDS

Mechanism	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Reassigned	FY 1995 Bud. Auth.	FY 1996 Estimate	FY 1997 Estimate
Research Project Grants	\$4,028,772	\$4,405,645	\$4,625,833	\$5,046,134	\$5,459,375	\$5,657,630	\$5,957,244	\$5,981,326	\$6,219,849	\$6,606,453	\$6,815,554
Research Centers	615,668	657,767	702,215	796,007	891,772	903,204	973,923	973,923	1,006,009	1,038,113	1,043,769
Other Research	394,980	441,349	493,953	546,136	561,400	547,837	542,705	518,621	504,330	551,697	551,138
Subtotal Research Grants	5,039,370	5,504,761	5,822,041	6,388,277	6,912,547	7,108,671	7,473,872	7,473,872	7,730,188	8,196,263	8,410,461
Research Training	262,941	283,015	318,896	342,260	348,018	350,805	372,688	372,688	390,546	395,343	404,975
R & D Contracts	532,446	583,495	630,487	664,698	705,821	693,508	765,249	765,249	723,178	770,749	763,636
Intramural Research	805,417	882,417	975,871	1,048,634	1,132,186	1,160,950	1,201,091	1,201,091	1,240,674	1,299,416	1,297,065
Res. Mgt. & Support	323,499	356,867	405,358	434,706	484,327	493,200	497,886	497,886	518,701	481,152	482,571
Cancer Control	69,682	74,100	75,433	85,390	107,569	105,283	145,900	145,900	192,275	225,000	227,500
Construction	0	31,345	16,322	7,349	12,000	7,528	23,421	23,421	17,963	23,000	2,000
Library of Medicine	67,700	78,798	81,663	91,182	102,937	103,496	117,783	117,783	127,869	141,439	146,579
Office of the Director	66,875	74,371	111,729	98,153	143,542	191,935	227,044	227,044	236,628	260,488	251,513
Subtotal	7,167,830	7,869,170	8,437,820	9,160,849	9,946,327	10,215,386	10,824,634	10,824,634	11,170,042	11,792,850	11,986,300
Buildings & Facilities	19,029	24,418	67,436	57,091	61,441	112,731	86,335	86,335	114,120	146,151	420,000
Total	7,186,959	7,893,588	8,505,256	9,217,940	10,010,368	10,328,117	10,910,969	10,910,969	11,284,162	11,939,001	12,406,300

NATIONAL INSTITUTES OF HEALTH

History of Actual Obligations*

FY 1998 - FY 1997

(Dollars in Thousands)

INCLUDES AIDS

INSTITUTE	FY 1998	FY 1999	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997
NCI	\$1,468,435	\$1,570,342	\$1,644,330	\$1,712,689	\$1,947,571	\$1,978,340	\$2,075,218	\$2,130,902	\$2,251,084	\$2,280,931
NHLBI	965,283	1,045,508	1,070,683	1,125,915	1,190,070	1,214,693	1,277,852	1,298,059	1,355,668	1,378,670
NIDR	126,216	130,689	135,432	148,691	158,900	161,116	169,490	174,845	183,198	186,781
NIDDK	534,359	559,274	579,964	615,262	661,446	680,514	715,622	735,726	771,252	784,923
NINDS	458,782	471,632	489,348	542,313	590,790	599,466	630,584	650,968	681,534	695,096
NIND	638,521	740,239	831,181	905,003	960,082	984,114	1,063,698	1,094,706	1,169,628	1,208,730
NIHMS	627,465	682,134	680,305	761,231	814,297	832,191	875,495	904,897	946,971	963,623
NIH	396,584	425,268	441,955	478,947	518,577	527,767	554,836	567,668	595,162	603,650
NIHSD	224,835	230,999	236,456	253,354	269,766	275,368	289,906	300,070	314,185	318,207
NIHES	215,439	223,309	228,725	240,606	251,464	251,047	264,111	272,062	288,898	295,142
NIA	184,548	222,545	238,927	323,791	382,862	399,523	420,266	433,879	453,917	463,365
NIAMS	147,543	159,896	168,538	193,449	203,516	212,208	223,160	232,001	242,828	247,141
NIDCD	75,081	94,275	117,283	134,957	148,748	154,655	162,782	168,690	178,502	180,816
NIHJ	327,514	384,928	440,222	511,967	560,285	582,851	613,352	628,921	661,293	671,205
NIDA	156,252	228,131	329,560	383,656	399,100	403,065	424,315	436,928	458,441	466,325
NIAAA	92,763	120,051	149,194	158,141	171,481	176,128	185,538	188,805	198,607	202,614
NIHJ	23,361	29,118	33,508	39,892	44,925	48,477	51,002	52,700	55,831	56,966
NIHJ	344,150	381,934	353,771	335,776	314,198	312,635	332,903	351,971	390,339	377,569
NCHGR	0	0	59,527	87,389	104,756	106,065	127,017	153,899	170,875	179,875
NIH	15,804	15,738	15,479	17,505	19,574	19,702	21,662	23,758	25,348	25,547
NLM	67,700	78,798	81,683	91,182	102,937	103,496	117,783	127,859	141,436	146,579
OD	68,875	74,371	111,729	98,153	143,542	191,935	227,044	238,628	260,468	251,513
Subtotal	7,167,930	7,869,170	8,437,820	9,160,849	9,948,927	10,215,386	10,824,634	11,170,042	11,792,850	11,986,300
B&F	19,029	24,416	67,436	57,091	61,441	112,731	86,335	114,120	146,151	420,000
TOTAL	7,186,959	7,893,586	8,505,256	9,217,940	10,010,368	10,328,117	10,910,969	11,284,162	11,939,001	12,406,300

* Obligations for actual years exclude lapses.

NATIONAL INSTITUTES OF HEALTH

History of Actual Obligations*

FY 1988 - FY 1997

(Dollars in Thousands)

EXCLUDES AIDS

INSTITUTE	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994	FY 1995 Bud. Auth.	FY 1996 Estimate	FY 1997 Estimate
NCI	\$1,378,491	\$1,448,095	\$1,494,026	\$1,551,800	\$1,781,903	\$1,805,311	\$1,863,201	\$1,913,167	\$2,025,294	\$2,080,382
NHLBI	940,398	1,007,420	1,028,627	1,079,509	1,143,864	1,168,635	1,222,875	1,242,574	1,297,941	1,320,565
NIDR	122,366	126,769	130,770	142,477	150,746	152,741	157,305	163,112	170,887	174,463
NIDDK	531,029	555,717	574,678	608,972	654,274	674,068	705,185	724,974	758,517	772,975
NINDS	446,450	458,563	473,190	525,662	563,198	581,050	608,471	628,247	657,727	671,148
NIAMD	415,223	428,962	438,098	475,063	511,142	524,416	520,764	536,940	573,610	584,362
NIGMS	671,741	671,304	665,691	745,643	798,197	815,341	851,552	880,233	920,836	936,573
NICHD	379,431	402,831	415,206	446,338	483,848	488,980	498,410	509,031	534,449	543,441
NEI	221,005	226,171	230,923	247,674	263,864	269,085	281,525	291,464	305,060	310,072
NIEHS	211,543	219,171	224,467	236,092	247,268	246,783	258,503	266,337	282,847	289,114
NIA	194,187	222,102	238,088	322,806	381,810	398,370	418,580	432,164	452,132	461,541
NIAMS	146,982	159,213	167,300	191,816	201,822	210,448	221,659	228,122	238,789	243,169
NIDCD	75,691	94,275	117,283	134,462	148,265	154,037	161,933	167,138	174,852	179,090
NIMH	298,326	336,555	376,891	438,247	484,145	504,418	526,170	540,570	567,737	578,149
NIDA	122,404	167,307	236,925	260,968	273,831	277,042	280,939	289,581	305,110	312,014
NIAAA	87,970	113,921	141,214	150,145	163,491	168,350	176,081	180,064	180,472	192,280
NINR	22,759	28,416	32,521	37,347	42,215	45,511	46,773	48,123	50,935	51,951
NCRR	315,867	314,318	307,624	286,347	264,147	261,754	271,520	287,341	321,989	309,344
NCHGR	0	0	59,527	87,369	104,756	106,095	126,380	152,906	169,041	177,788
FIC	11,089	11,120	10,581	12,154	13,981	14,018	12,810	14,560	15,654	15,790
NLM	67,700	78,778	81,190	90,663	101,860	102,395	115,001	125,195	138,277	143,268
OD	61,238	61,506	101,445	86,416	128,429	177,354	202,508	214,234	233,880	226,913
Subtotal										
B&F	18,659	18,644	54,566	52,125	53,883	108,978	86,335	114,120	146,151	420,000
TOTAL	6,686,590	7,151,158	7,900,801	8,213,115	8,960,759	9,254,180	9,614,498	9,950,287	10,531,177	10,874,352

* Obligations for actual years exclude lapse.

NATIONAL INSTITUTES OF HEALTH

History of Actual Obligations*

FY 1988 - FY 1997

(Dollars in Thousands)

AIDS ONLY

INSTITUTE	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994	FY 1995 Bud. Auth.	FY 1996 Estimate	FY 1997 Estimate
NCI	\$89,944	\$122,247	\$150,304	\$160,869	\$165,668	\$173,029	\$213,017	\$217,735	\$225,760	\$220,539
NHLBI	24,885	38,088	42,056	46,405	46,206	48,058	54,977	55,485	57,925	56,115
NIDR	3,850	3,920	4,662	6,214	6,154	6,375	12,185	12,309	12,318	12,318
NIDDK	3,330	3,557	5,306	6,290	7,172	6,446	10,437	10,752	11,735	11,948
NINDS	12,342	13,088	16,158	16,651	17,592	18,416	22,113	22,741	23,807	23,960
NIAD	223,298	311,277	363,083	430,940	448,940	459,698	542,912	557,766	596,018	624,368
NIGMS	7,724	10,830	14,614	15,568	16,100	16,850	23,943	24,664	26,135	27,050
NICHD	17,153	22,437	26,749	32,609	34,729	38,807	56,426	58,667	60,713	60,209
NEI	3,830	4,828	5,533	5,680	5,902	6,283	8,381	8,608	9,125	8,135
NIHES	3,696	4,136	4,258	4,514	4,216	4,264	5,608	5,745	6,051	6,028
NIA	361	443	859	985	1,072	1,153	1,686	1,715	1,785	1,824
NIAMS	561	673	1,238	1,633	1,694	1,760	1,501	3,879	4,039	3,672
NIDCD	0	0	0	495	483	618	849	1,552	1,650	1,726
NIH	31,188	48,373	63,331	72,720	76,140	78,433	87,182	89,351	93,556	93,056
NIDA	33,848	60,824	92,635	122,688	125,268	126,023	143,376	147,347	153,331	154,311
NIAAA	4,793	6,130	7,980	7,986	7,980	6,778	9,457	9,741	10,135	10,334
NIH	602	702	987	2,545	2,710	2,966	4,228	4,577	4,896	5,015
NCRR	28,263	67,616	46,147	47,429	50,051	50,881	61,383	64,630	68,370	68,255
NCHGR	0	0	0	0	0	0	637	993	1,000	2,067
FIC	4,505	4,619	4,898	5,351	5,593	5,684	8,852	8,108	9,894	9,757
NLM	0	20	483	519	1,057	1,101	2,782	2,694	3,162	3,311
OD	5,636	12,865	10,264	11,737	15,113	14,581	24,538	24,364	26,598	24,600
Subtotal										
B&F	370	5,772	12,880	4,968	7,756	3,753	0	0	0	0
TOTAL	500,389	742,426	904,455	1,004,825	1,049,606	1,073,957	1,298,471	1,333,875	1,407,824	1,431,908

* Obligations for actual years exclude lapse

NATIONAL INSTITUTES OF HEALTH

Justification

Management Fund

General Statement

The NIH Management Fund (MF) was established on June 29, 1957, by Public Law 85-67. The MF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The expenses for these activities are paid by the NIH appropriations and other government agencies. The services provided by the MF include utilities and plant maintenance, a 500 bed hospital and outpatient clinic, receipt, review and referral of research and training grant applications, collaborative computer science research and biomedical engineering, and general administrative support services.

To promote the stability of Clinical Center funding and to enable the Clinical Center to operate more efficiently, the following changes are proposed: 1) core Clinical Center costs shall be assessed to the Institutes on the basis of historical usage; 2) NIH shall be authorized to collect third party payments for the cost of clinical services that are incurred in National Institutes of Health research facilities and that such payments shall be credited to the National Institutes of Health Management Fund; and 3) all funds credited to the NIH Management Fund shall remain available for one fiscal year after the fiscal year in which they are deposited.

NATIONAL INSTITUTES OF HEALTH

Management Fund

Obligations By Activity
(dollars in thousands)

	1995 Actual		1996 Estimate		1997 Estimate	
	<u>FTEs</u>	<u>Amount</u>	<u>FTEs</u>	<u>Amount</u>	<u>FTEs</u>	<u>Amount</u>
Computer services.....	124	\$21,262	121	\$25,717	121	\$25,717
Intramural scientific services.....	207	25,176	220	25,430	220	25,430
Clinical services.....	1,939	216,626	1,890	223,731	1,890	223,731
Grant review and services.....	407	40,929	399	41,160	399	41,160
Intramural research support services.....	757	133,008	734	138,627	734	138,627
Rental payments.....	--	24,163	--	26,414	--	26,414
Total Obligations.....	3,434	461,164	3,364	481,079	3,364	481,079

NATIONAL INSTITUTES OF HEALTH

Management Fund

Source of Income

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
NCI.....	\$134,940,000	\$141,755,000	\$139,960,000
NHLBI.....	48,869,000	49,257,000	48,182,000
NIDR.....	8,516,000	9,227,000	9,022,000
NIDDK.....	27,827,000	28,329,000	28,010,000
NINDS.....	33,276,000	34,934,000	34,301,000
NIAID.....	32,510,000	35,502,000	35,315,000
NIGMS.....	7,679,000	7,882,000	7,742,000
NICHD.....	26,594,000	25,257,000	25,615,000
NEI.....	10,115,000	10,608,000	11,594,000
NIEHS.....	2,621,000	3,295,000	3,185,000
NIA.....	7,134,000	7,798,000	7,840,000
NIAMS.....	7,989,000	8,828,000	8,636,000
NIDCD.....	2,992,000	3,510,000	3,559,000
NIMH.....	32,995,000	32,099,000	34,800,000
NIDA.....	655,000	746,000	2,802,000
NIAAA.....	6,608,000	6,357,000	6,220,000
NCRR.....	5,266,000	4,142,000	3,772,000
NINR.....	1,002,000	1,186,000	1,118,000
NCHGR.....	3,815,000	6,161,000	6,267,000
FIC.....	1,359,000	1,463,000	1,367,000
NLM.....	9,249,000	10,053,000	10,797,000
FDA.....	7,099,000	7,425,000	8,450,000
SSF.....	<u>10,957,000</u>	<u>10,534,000</u>	<u>7,794,000</u>
SUBTOTAL	430,067,000	446,348,000	446,348,000
INTRAFUND			
BILLING.....	26,727,000	27,300,000	27,300,000
DIRECT			
REIMBURSEMT.	<u>6,831,000</u>	<u>7,431,000</u>	<u>7,431,000</u>
	463,625,000	481,079,000	481,079,000

NATIONAL INSTITUTES OF HEALTH

Management Fund

Budget Authority by Object

	1996 Appropriation	1997 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	3,364	3,364	0
Full-time equivalent of overtime and holiday hours	138	129	-9
Average ES salary	\$111,305	\$114,313	+\$3,008
Average GM/GS grade	10.3	10.3	
Average GM/GS salary	\$40,016	\$40,908	+892
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	62,990	64,870	+1,880
Average salary of ungraded positions	32,062	33,024	+962
Full-time permanent	\$140,534,000	\$140,929,000	+\$395,000
Other than full-time permanent	12,566,000	12,605,000	+39,000
Other personnel compensation	10,625,000	10,631,000	+6,000
Special personnel services	1,513,000	1,537,000	+24,000
Subtotal Personnel Compensation	165,238,000	165,702,000	+464,000
Personnel benefits	37,135,000	37,262,000	+12,7000
Benefits for former personnel	1,130,000	1,130,000	0

	1996 Appropriation	1997 Estimate	Increase or Decrease
Travel and transportation of persons	1,249,000	1,246,000	-3,000
Transportation of things	895,000	894,000	-1,000
Rent, communications and utilities	64,345,000	64,265,000	-80,000
Printing and reproduction	2,662,000	2,661,000	-1,000
Other services	151,567,000	151,152,000	-415,000
Supplies and materials	39,108,000	39,092,000	-16,000
Equipment	<u>17,750,000</u>	<u>17,675,000</u>	<u>-75,000</u>
TOTAL	481,079,000	481,079,000	0

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

CENTRAL SERVICES
Program Administration
Detail of End-of-Year Employment
Management Fund

	1995 Actual	1996 Estimate	1997 Request
Executive level I	0	0	0
Executive level II	0	0	0
Executive level III	0	0	0
Executive level IV	0	0	0
Executive level V	0	0	0
Subtotal	0	0	0
Total - Executive Level Salary			
ES-6	0	0	0
ES-5	1	1	1
ES-4	3	3	3
ES-3	3	3	3
ES-2	1	1	1
ES-1	0	0	0
Subtotal	8	8	8
Total - ES Salary	\$868,504	\$890,443	\$914,504
GS/GM-15	83	90	90
GS/GM-14	191	179	179
GS/GM-13	198	193	193
GS-12	325	317	317
GS-11	358	358	355
GS-10	382	373	373
GS-9	198	204	204
GS-8	93	100	100
GS-7	296	287	287
GS-6	201	196	196
GS-5	196	195	195
GS-4	133	131	131
GS-3	37	36	36
GS-2	20	20	20
GS-1	4	4	4
Subtotal	2,715	2,683	2,680

Assistant Surgeon General.....	7	7	7
Director Grade.....	53	52	52
Senior Grade.....	55	54	54
Full Grade.....	41	40	40
Senior Assistant Grade.....	29	28	28
Assistant Grade.....	20	20	20
Co-Step.....	2	2	2
Subtotal	207	203	203
Ungraded.....	543	517	517
Total Permanent Positions.....	3,404	3,368	3,368
Total Position, end of year	6,877	6,779	6,776
Total full-time equivalent (FTE) employment, end of year	3,434	3,364	3,364
Average ES Level	3.5	3.5	3.5
Average ES salary	\$108,563	\$111,305	\$114,313
Average GS/GM grade	10.1	10.3	10.3
Average GS/GM salary	\$39,019	\$40,016	\$40,908

NATIONAL INSTITUTES OF HEALTH

Justification

Service and Supply Fund

General Statement

The NIH Service and Supply Fund (SSF) was established on April 11, 1953, under 42 U.S.C. 231. The SSF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The SSF provides a single means for consolidating the financing and accounting of business-type operations involving the sales of services and commodities to customers. The services provided by the SSF include mainframe computing, engineering planning and design, printing, telecommunications, procurement, shipping and receiving, motor pool, research animals, fabrication and maintenance of scientific equipment, and other administrative support services.

The NIH intends to hold FY 1997 total Service and Supply Fund obligations at the FY 1996 estimated level of \$260,797,000 through consolidating and streamlining operations where possible; increasing the efficiency and productivity of employees through planned training and automation of processes; and to further explore ways that fewer FTEs can still support NIH programs.

NATIONAL INSTITUTES OF HEALTH

Service and Supply Fund

Budget Authority by Object

	<u>1996 Estimate</u>	<u>1997 Estimate</u>	<u>Increase or Decrease</u>
Total compensable workyears:			
Full-time employment	1,086	1,086	0
Full-time equivalent of overtime and holiday hours	45	46	+1
Average ES salary	\$116,689	\$120,306	+\$3,617
Average GM/GS grade	10.6	10.6	
Average GM/GS salary	\$41,683	\$42,557	+\$874
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	63,000	64,890	+1,890
Average salary of ungraded positions	33,290	33,956	+666
Full-time permanent	\$44,952,000	\$45,910,000	+\$958,000
Other than full-time permanent	822,000	841,000	+19,000
Other personnel compensation	3,321,000	3,380,000	+59,000
Special personnel services	0	0	0
Subtotal Personnel Compensation	49,095,000	50,131,000	+1,036,000
Personnel benefits	9,091,000	9,309,000	+218,000
Benefits for former personnel	703,000	703,000	0

	1996 Estimate	1997 Estimate	Increase or Decrease
Travel and Transportation of persons ...	584,000	505,000	-79,000
Transportation of things	2,403,000	2,296,000	-107,000
Rent, communications and utilities	40,018,000	39,563,000	-455,000
Printing and reproduction	4,893,000	4,691,000	-2,000
Other services	93,617,000	93,291,000	-326,000
Supplies and materials	51,384,000	51,376,000	-8,000
Equipment	9,209,000	8,932,000	-277,000
TOTAL	260,797,000	260,797,000	0

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
Service and Supply Fund
Obligations By Activity
(dollars in thousands)

	1995 Actual		1996 Estimate		1997 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Administrative Services:						
Cost of Goods Sold.....		\$39,695		\$39,995		\$39,995
Other.....	697	145,298	774	138,357	774	138,357
Data processing services..	176	51,137	171	53,778	171	53,778
Instrumentation:						
Cost of Goods Sold.....		4,567		4,529		4,529
Other.....	58	8,378	69	8,244	69	8,244
Research animals.....	66	16,110	72	15,894	72	15,894
Total Obligations.....	997	265,185	1,086	260,797	1,086	260,797

CENTRAL SERVICES
Program Administration
Detail of End-of-Year Employment
Service and Supply Fund

	1995 Actual	1996 Estimate	1997 Request
Executive level I	0	0	0
Executive level II	0	0	0
Executive level III	0	0	0
Executive level IV	0	0	0
Executive level V	0	0	0
Subtotal	0	0	0
Total - Executive Level Salary			
ES-6	0	0	0
ES-5	0	0	0
ES-4	2	2	2
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	2	2	2
Total - ES Salary	\$226,360	\$233,377	\$240,612
GS/GM-15	19	23	16
GS/GM-14	43	48	37
GS/GM-13	115	122	104
GS-12	115	125	135
GS-11	76	91	109
GS-10	5	5	13
GS-9	64	76	63
GS-8	28	31	30
GS-7	84	101	98
GS-6	58	63	72
GS-5	41	45	44
GS-4	29	32	29
GS-3	7	7	19
GS-2	0	0	0
GS-1	0	0	0
Subtotal	684	769	769

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Assistant Surgeon General.....	1	1	1
Director Grade.....	4	4	4
Senior Grade.....	6	6	6
Full Grade.....	1	1	1
Senior Assistant Grade.....	0	0	0
Assistant Grade.....	0	0	0
Co-Step.....	0	0	0
Subtotal	12	12	12
Ungraded.....	240	252	252
Total Permanent Positions.....	968	1,060	1,060
Total Position, end of year	1,906	2,095	2,095
Total full-time equivalent (FTE) employment, end of year	997	1,086	1,086
Average ES Level	4.0	4.0	4.0
Average ES salary	\$113,180	\$116,689	\$120,306
Average GS/GM grade	10.6	10.6	10.6
Average GS/GM salary	\$40,863	\$41,683	\$42,557

FRIDAY, APRIL 19, 1996.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

WITNESSES

DR. CLAUDE LENFANT, M.D., DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

DR. BARBARA PACKARD, M.D., ASSOCIATE DIRECTOR FOR SCIENTIFIC PROGRAM OPERATIONS

JAMES WEHLING, FINANCIAL MANAGEMENT OFFICER

SHEILA MERRITT, EXECUTIVE OFFICER

DR. HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We continue today with the hearings of the Department of Health and Human Services, and specifically of the Institutes which comprise the National Institutes of Health. And we're pleased to welcome today Dr. Lenfant, the Director of the National Heart, Lung, and Blood Institute. And Dr. Lenfant, why don't you introduce the people with you at the table and then proceed.

INTRODUCTION OF WITNESSES

Dr. LENFANT. Thank you very much, Mr. Chairman.

On my far left is Ms. Merritt, who is our new, and I underscore new, Executive Officer, and it gives me great pleasure to introduce her to you. Mr. Wehling, whom you have seen many times, our Financial Management Officer. Dr. Packard, who is the Associate Director for Scientific Programs, and of course Dr. Varmus and Mr. Williams from the Department.

OPENING STATEMENT

I am very pleased to be here today, Mr. Chairman, to tell you about our progress, but also to underscore some of the issues which are before us. Since I last appeared before you, we have completed a number of clinical trials, which I describe in detail in my statement. But I would like to make some comments about them.

The fact is, clinical trials give us the opportunity to make further progress in the decline of cardiovascular disease, as they give us new treatments and new approaches to prevention. The decline in heart disease is illustrated in this chart, which shows the most common cardiovascular heart disease, heart attack. And as you can see, we have had during the last 30 years a very significant decrease in mortality rates from this condition.

HEART FAILURE

Coming back to the clinical trials, I also would like to underscore that they give us a great potential for considerable cost savings in the treatment of these patients. However, while we may have seen this decline in cardiovascular diseases, and especially coronary heart disease and heart attack, we're also seeing a very sharp upturn in the public health burden of congestive heart failure, that many in the scientific community call the new epidemic of cardiovascular disease.

I have reported to you in past years about the upturn of this condition. But since, we have accumulated new data, which I would like to present to you. In the next chart, you will see the increase in the annual number of hospitalizations from this condition, congestive heart failure. And in the next one, you will see the increase in the annual number of deaths coming from this condition.

I have to say that we have made very significant progress during the last few years, to bring down the increase in the number of hospitalizations and even delayed to some extent the occurrence of death in these patients. But as yet, we are really facing tremendous public health problems.

Today, there are approximately 4.7 million Americans who are suffering from this condition. Of course, this number is very worrisome, but in my view, not as much as two facts which I would like to underscore for you, and that you will see in the next chart. As you can see, comparing the blue and the red lines, the number of people affected by this condition has more than doubled during the last ten years. The blue line represents the prevalence of this condition in the dates 1976 to 1980, and the red line shows the prevalence of this condition from the late 1980s and early 1990s.

[The information follows:]

Prevalence of Heart Failure



Source: National Health and Nutrition Examination Surveys II and III.

Dr. LENFANT. The second fact which is depicted in this chart is that, contrary to the common belief, this condition is not one of the elderly only. Indeed, there is a huge number of Americans suffering from these conditions in the prime years of their lives. As you can see the number is very high and quite significant in their 50s. And considering that these people, according to longevity in this country, have, or would have, 25 to 30 years ahead of them, we have to be concerned by the appearance of these conditions in such a young population.

The good news about all that is that there are some recent developments in cellular and molecular approaches which offer some very exciting and promising strategies to restore the heart functions in these patients. But I must tell you, Mr. Chairman, that this research, which I believe will be very fruitful in time, is going to be slow and it will be costly. However, I should underscore that the cost of this research will be far less expensive than caring for the ever-increasing number of the patients developing this disease.

ASTHMA

Before concluding these remarks, I would like to say some words about asthma, which is another public health burden, which affects nearly 12 million to 14 million Americans, from the very old to the very young. As you can see in the next chart, the death rate of asthma, although low, is increasing, especially in the African-American community. Our research, which is quite intense, has been quite successful during the last few years, and especially this year, in the sense that we have uncovered two genes which have opened the process for understanding this condition.

These findings are truly of importance in the sense that they open the door to the development of better techniques for early diagnosis and prevention of this disease. And as well, new approaches for its treatment.

I had planned to say a few words about our blood program, but I was very pleased that yesterday, Dr. Varmus, in his introductory remarks, mentioned one of the very significant discoveries that appeared in our blood program this year, that is, the discovery of a new function for hemoglobin, and the impact of this discovery is quite significant in the blood community as well as the cardiovascular community. It is really exciting and we think we have prospects for some very important findings in the years to come.

In closing, Mr. Chairman, I would like to mention some of the innovations to streamline our operations and to make better use of our resources. We have considerably improved our peer review system in our Institute, we have simplified application procedures to save considerable expenses for both investigators and the Institute. The Institute has been entirely reorganized, developing into a much flatter organization, which makes us much more effective.

And finally, in support to the NIH-wide effort to streamline, the Institute now has taken up the responsibility to become a service center for three key areas of NIH operation, we are providing a service for other Institutes and thereby reducing some of the staff requirements for the NIH as a whole.

This concludes my remarks, Mr. Chairman, and I will be pleased to answer any questions.

[The prepared statement and biography of Dr. Claude Lenfant follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES**National Institutes of Health****Statement of the Director
National Heart, Lung, and Blood Institute**

I am pleased to address the committee once again on behalf of the National Heart, Lung, and Blood Institute (NHLBI). Let me begin by reporting some findings from four clinical trials that have immediate applicability to medical practice. Each is significant not only because it points the way to improved treatment or prevention of widespread diseases, but also because it is expected to yield considerable cost savings.

The Bypass Angioplasty Revascularization Investigation found that using balloon angioplasty to relieve severe coronary artery blockages provides most patients with long-term health benefits comparable to those of coronary artery bypass grafting (CABG) surgery, which is much more invasive and, therefore, more expensive. However, the trial found that heart patients taking medication for diabetes fared much better with CABG. Five years after the procedure, 81 percent of CABG patients, but only 65 percent of angioplasty patients, were still alive. Thus, we have conclusive evidence that the expense and discomfort of CABG are worthwhile in this subset of diabetic patients.

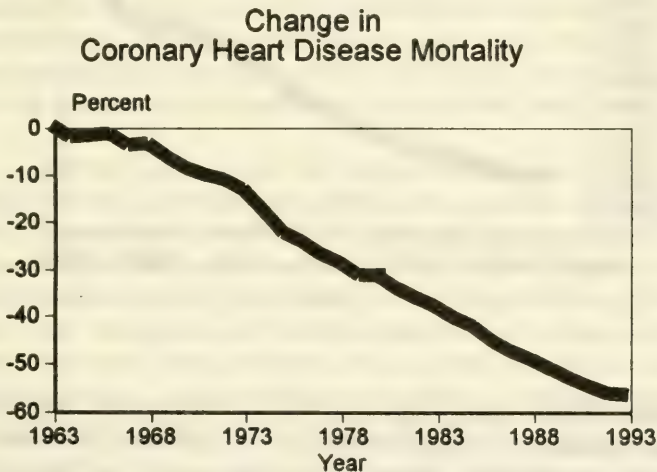
Most CABG is performed using a length of vein taken from elsewhere in the body to bypass the blocked coronary artery. However, 30 to 40 percent of these venous grafts themselves clog up a decade after surgery, mainly due to an accelerated form of atherosclerosis. The Post-CABG Clinical Trial found that aggressive cholesterol-lowering treatment after CABG slowed the pace of atherosclerosis, reduced the need for additional revascularization procedures, and lowered heart attack and death rates. These results provide convincing evidence that a fairly simple intervention can enhance the long-term benefit of CABG surgery.

Although the well-known drug digitalis has been used since the 17th century to treat heart failure, its efficacy was rigorously tested only recently in an NHLBI clinical trial done in collaboration with the Veterans Administration. The study found that, while digitalis did not extend the lives of heart failure patients, it did lessen their symptoms and, therefore,

their need for hospitalization. Because heart failure is the leading cause of hospitalizations among Americans over 65 years of age, these findings have major cost implications.

Finally, the second phase of the Trials of Hypertension Prevention demonstrated convincingly that long-term prevention of hypertension is achievable through a strategy of weight loss and sodium reduction. Because treatment of hypertension reduces, but does not entirely eliminate, the serious consequences of this disorder, hypertension prevention is a major public health priority. These findings will bring us closer to achieving that goal, particularly if societal changes to facilitate maintenance of these lifestyle changes can be achieved.

These results are but the latest chapter in the story of our continuing efforts to improve treatment and prevention of disease--efforts that have successfully halved mortality from coronary heart disease over

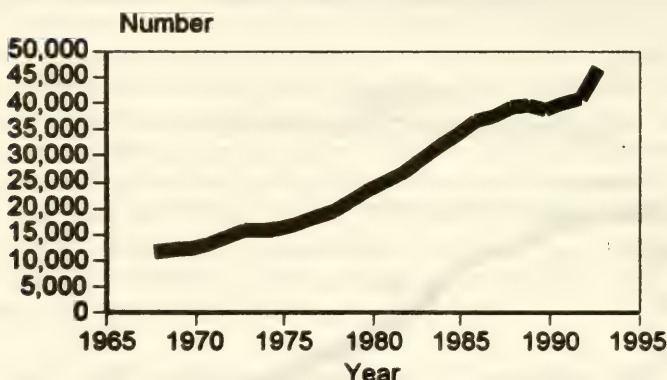


the last few decades and reduced stroke deaths by 60 percent. However, we must not grow complacent in the face of these achievements. Mr. Chairman, when I appeared before this committee last year, the first question you asked about the Institute was the following: "Do you think that you are a victim of your own success?" That is the crux of the matter that I wish to bring to your attention today.

We are, indeed, pleased to have forestalled so many premature deaths, especially those due to coronary heart disease, but several substantial tradeoffs must be acknowledged. One is that public concern about cardiovascular diseases as major killers has lessened--a situation that may, in turn, reduce emphasis on primary preventive efforts such as staying fit and eating a healthy diet, and may also lead to neglect of the early symptoms of heart attack.

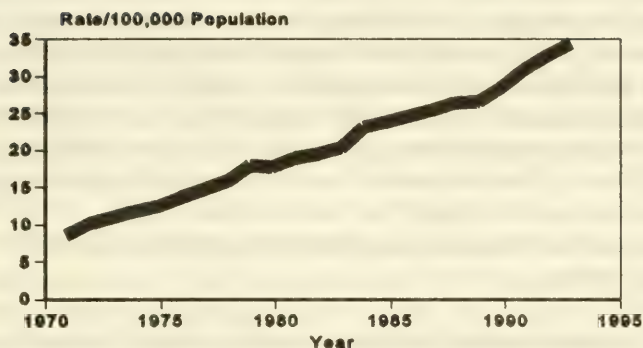
The second repercussion is a sharp upturn in the public health burden of congestive heart failure, as measured by both deaths and hospitalizations. Heart failure represents the final, devastating

Annual Heart Failure Deaths



complication of many other forms of cardiovascular diseases. Its victims--all told, an estimated 4.7 million Americans--are survivors of coronary heart disease, hypertension, diseases of the heart muscle, and valvular and congenital malformations, whose overburdened hearts can no longer pump effectively. Heart failure can drag on for years, leaving the patient exhausted and bedridden, yo-yoing between home and hospital. Death becomes inevitable when organ systems give out under the burden of oxygen deprivation. It is a miserable way to live and a hard way to die.

Hospitalization Rates for Heart Failure



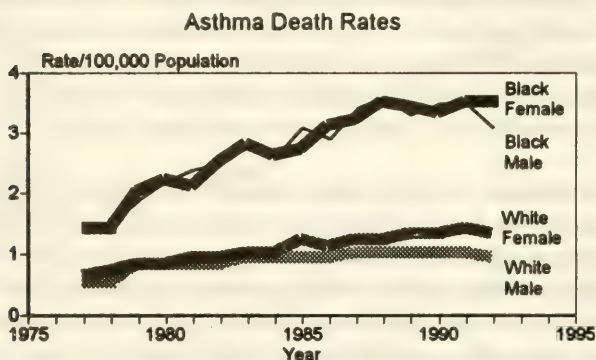
Clinical research, such as the aforementioned digitalis study, has identified helpful strategies for treating heart failure. However, the magnitude and complexity of the problem demand that we bring the full armamentarium of modern basic science to bear on it. Recent developments in cellular and molecular techniques offer particularly exciting promise for new strategies to restore heart function.

For instance, we know that various forms of injury, including heart attack, lead to the death of individual cardiac myocytes (heart muscle cells). Because adult cardiac myocytes cannot reproduce, their loss leads to heart failure. However, new studies raise the possibility that heart cell transplantation may be a feasible and effective approach to replacing these cells. First using mice, and then extending the work to dogs, researchers have shown that cardiac myocytes can be grafted from embryonic donors into adult hearts. The transplanted cells appear to become part of the recipient's heart tissue and to function normally.

This cellular transplantation technique could be augmented through gene transfer technology to enhance cardiac myocyte function. Recent experiments using transgenic and gene targeting methods to create genetically altered mice suggest that a number of promising targets exist to improve the heart's pumping ability.

We have also reached a new frontier in the area of heart transplantation. Although transplantation of human hearts is an effective treatment for end-stage heart failure, a major drawback is the shortage of donor organs. Recent developments using transgenic methods are now breaking down the barriers to using animal organs in human bodies. Specifically, transgenic pigs have been engineered to produce human proteins that suppress the body's immediate tendency to reject the "foreign" heart. When the hearts of such pigs were transplanted into baboons, they survived longer than had ever been possible. With further development, this "futuristic" approach to the problem of heart failure may become a reality.

The new molecular and genetic tools are also advancing our understanding of asthma, a long-term chronic disease whose death rate, though low, is increasing in the United States. Asthma appears to be



strongly influenced by the interplay of genetic and environmental factors, and we are rapidly gaining insight into this phenomenon. Scientists have now uncovered the location of major genes that control airway hyperreactivity and allergy, two important risk factors for asthma. The genes are located in regions of chromosome 5 that are rich in cytokines, molecules that are thought to regulate the process of inflammation that leads to development of asthma. In parallel studies, a large number of families with well-defined asthma are being characterized in an attempt to identify all the genes that confer susceptibility to asthma. Scientists will then proceed to examine more closely specific genes of interest.

These findings represent the first important step in unraveling the genetic basis of asthma. With the genes in hand, it will then be possible to explore their interactions with environmental factors that play such an important role in causing the disease. Identification of the genes responsible for allergy and asthma is expected to lead to a better understanding of the primary defects in asthma, to development of better techniques for early diagnosis and disease prevention, and to new approaches for treatment.

Similarly, much progress is being made in understanding the genetic basis of hypertension. Scientists have discovered the genes responsible for two rare forms of hypertension that strike early in life and are inherited in a simple, Mendelian fashion. As a result, it is now possible offer a genetic test to patients with a strong family history of early-onset hypertension, and to target therapy to the underlying disorder. In addition, these discoveries offer important clues for deciphering the more complex "essential" hypertension that strikes millions of Americans.

Application of new basic science approaches is also advancing the possibility that blood stem cells may be used instead of bone marrow to treat acquired and inherited blood diseases. Researchers are currently working on methods to prepare pure populations of stem cells and expand their numbers, to control "homing" mechanisms by which they take root in the bone marrow, and to insert normal genes into them. This work is receiving active attention by many researchers around the country, who are optimistic that cures for hematologic and other diseases are within reach.

Finally, genetic and molecular mechanisms of sleep constitute one of the most promising frontiers for sleep research. Evidence is mounting that circadian rhythm, the "biological clock" that determines our patterns of sleep and wakefulness, is controlled by genes; indeed, several such genes have been found in animals. A better understanding of the molecular basis of normal and abnormal sleep is expected to have a strong impact on traffic accidents, worker absenteeism, and other public burdens caused by sleep disorders.

In closing, let me mention our innovations to streamline our operations and make better use of our resources. In our peer review of grants, for example, we have simplified application procedures to save time and expense for both investigators and the Institute. The NHLBI now functions as a service center for three key areas of NIH operations, thereby

reducing staffing requirements. Finally, we have been in the forefront of efforts to use paperless methods of communication with the scientific community and the public.

Mr. Chairman, the FY 1997 budget request for the NHLBI is \$1,320,555,000. I would be pleased to answer any questions that the committee may have.

March 1996

LENFANT, CLAUDE, M.D.Director, National Heart, Lung,
and Blood Institute, NIH

October 12, 1928, Paris, France

Education: B.S., University of Rennes, France, 1948. M.D., University of
Paris, France, 1956.Professional History: 1957-1958, Research Fellow, University of Buffalo,
New York. 1958-1959, Research Fellow, Columbia University, New
York. 1959-1960, Assistant Professor of Physiology, University of Lille,
France. 1961-1965, Clinical Instructor of Medicine and of Physiology and
Biophysics, University of Washington, Seattle. 1966-1967, Clinical
Assistant Professor of Medicine and of Physiology and Biophysics,
University of Washington, Seattle. 1968-1971, Associate Professor of
Medicine and Physiology and Biophysics, University of Washington,
Seattle. 1970-1972, Acting Associate Director, Collaborative R&D
Program, National Heart and Lung Institute, NIH. 1970-1972, Associate
Director for Lung Programs, National Heart and Lung Institute, NIH.
1971-1972, Professor of Medicine and Physiology and Biophysics,
University of Washington, Seattle. 1972-1980, Director, Division of Lung
Diseases, National Heart, Lung, and Blood Institute, NIH. 1981-1982,
Associate Director for International Research, NIH. 1981-1982, Director,
Fogarty International Center for Advanced Study in the Health Sciences,
NIH. 1982-Present, Director, National Heart, Lung, and Blood Institute,
NIH.Professional Organizations: Association of American Physicians, American
Society for Clinical Investigation, American Physiological Society,
American Federation for Clinical Research, French Physiological Society,
International Federation for Medical Electronics, American Society of
Zoologists, Society for Experimental Medicine and Biology, Undersea
Medical Society, New York Academy of Science.Honors, Awards: Thesis Prize, University of Paris, France, 1956.
Commendation Tohoku Medical Society, Sendai, Japan, 1973. Superior
Service Honor Award, DHHS, 1974. Regents' Professor, University of
California, Los Angeles, 1975. Testimonial Dinner, American Thoracic
Society, 1979. Honorary Fellow, American College of Chest Physicians,
1979. Honorary Professor, National Yang-Ming Medical College Taipei,

Taiwan, 1980. Honorary Professor, Universidad Peruana Cayetano Heredia, Lima, Peru, 1981. Senior Executive Service Performance Award, 1982. Elected Institute of Medicine, National Academy of Sciences, 1983. American Heart Association Scientific Councils' "Distinguished Achievement Award," 1983. Senior Executive Service Performance Award, 1983. Honorary Fellow Council on Clinical Cardiology - American Heart Association, 1984. Senior Executive Service Performance Award, 1984. Forrest M. Bird Contributory Award, American Respiratory Therapy Foundation, 1985. Senior Executive Service Performance Award, 1985. Presidential Meritorious Executive Rank Award, 1987. Elected Honorary Member, Royal Society of Medicine, England, 1988. Honorary Doctor of Science, State University of New York, Buffalo, 1988. Elected Member, USSR (now Russia) Academy of Medical Sciences, 1988. Cystic Fibrosis Foundation "Breath of Life" Award, 1988. Elected Honorary Member, French Cardiology Society, 1989. Senior Executive Service Performance Award, 1989. Brotherhood Award - Association of Black Cardiologists, 1990. Appointed, Board of Governors, US-Israel Binational Science Foundation, 1990-1993, Senior Executive Service Performance Award, 1990. Presidential Distinguished Executive Rank Award, 1991. Elected Fellow, Royal College of Physicians (London, England), 1992. Senior Executive Service Performance Award, 1992. 1992 Federal Executive of the Year Award. Elected Member, French National Academy of Medicine, 1993. Surgeon General's Exemplary Award, 1993. Senior Executive Service Performance Award, 1993. Special Recognition Award - American Academy of Allergy and Immunology, 1994. Giovanni Lorenzini Foundation Prize for the Advancement of Biomedical Science, 1994. Senior Executive Association's Executive Excellence Award for Distinguished Executive Service, 1994. Senior Executive Service Performance Award, 1994. Laura Graves Award - National Marrow Donor Program, 1995. Senior Executive Service Performance Award, 1995. Consortium of Southeastern Hypertension Centers' Excellence in Leadership Award, 1995.

Authorship, Editorship: Author or Co-Author of 224 scientific publications Served on Editorial Boards of: Am. Journal of Physiology; Journal of Applied Physiology; Respiratory Physiology; Am. Review of Respiratory Disease; Undersea Biomedical Research; Proceedings of Society for Experimental Biology and Medicine; Revue Francaise des Maladies Respiratoires; Journal of Applied Physiology; Respiration, Environmental and Exercise Physiology; Am. Journal of Medicine; Continuing Education for Family Physicians; Executive Editor of 90 volumes for monograph series, "Lung Biology in Health and Disease."

NHLBI BUDGET INCREASE

Mr. PORTER. Thank you, Dr. Lenfant.

We also want to welcome Dr. Varmus once again. And I want to welcome my colleague from Florida, Dan Miller. I expected I would be here alone today, because the House is not in session. But we're glad to see you, Dan.

Dr. Lenfant, I had hoped to slip in this question before Dr. Varmus appeared, but—

[Laughter.]

Mr. PORTER. What do you say to those people who look at your budget over a period of time and say, relative to other institutes, your Institute is not getting the rate of increase that others are? Is this because the things you work on are less important? What would you say to those people, and why is this happening?

Dr. LENFANT. Well, I will begin my response taking into consideration the fact that Dr. Varmus has appeared. [Laughter.]

Dr. VARMUS. I would assume you would answer honestly in either case. [Laughter.]

Dr. LENFANT. I would say that, first of all, I would certainly oppose the notion that the work which is conducted in the areas of interest of the Institute is less important than others. I would be sad, actually, to hear that some people make such a statement.

Mr. PORTER. Actually, I haven't heard anybody make that statement. I heard a lot of people make the opposite statement, that you're not getting enough funding because your Institute's areas are more important.

Dr. LENFANT. Well, I'm glad we both agree on this point. The Institute is one of 24 institutes, and there are many issues which are confronting the NIH as a whole, and the public health in this country.

And, personally I do not believe, in contrast to what is believed by many, that the allocation of funds should be based on the death rate from a condition. I think that the allocation of funds should be on the basis of where the state of the science is, on the basis of the morbidity of the condition, and on the basis of the cost, if you will, of this condition to the country and the health care system.

There is no question that the cardiovascular diseases rank very high; the cost to the country for the care of cardiovascular diseases is estimated at approximately \$120 billion a year, which is a very significant cost. In terms of morbidity, there are millions of people who are suffering from this condition. I have depicted earlier the situation for one such condition.

And in terms of opportunities within the Institute and what's going on in cardiovascular disease, I have mentioned in my opening statement and written statement some of the avenues which are pursued to address the issue of congestive heart failures. And that is only one example.

But I'm trying to say that we are at the forefront of what's going on. But so are other areas of research. And Dr. Varmus makes his decision and I respect the decision.

HEART FAILURE

Mr. PORTER. Let me ask you about heart failure. Those people who, like myself, don't know much about this would say heart failure is kind of a catch-all. If you're going to die of something, then it isn't anything else that you can identify, it's heart failure, supposedly. But I don't know that I'm at all close to the truth in that. Could you explain how you define heart failure?

Dr. LENFANT. Okay. Heart failure results from a weakening of the heart. The heart is made up of muscle, and the muscle is made up of a great number of cells. And following a number of conditions, which can be heart attack, which can be hypertension, which can be a defect in the valves which are in the heart, eventually this heart muscle weakens and is no longer able to provide all the organs in the body with the oxygen and the nutrients which are transported by the blood. And basically, the people who are suffering from this condition are tremendously handicapped and unable to perform in a normal fashion.

The point that I think addresses your question is that as I showed in the chart which is on the floor now—would you put it back up? This condition, contrary to the belief, which seems to be quite—yes, this one—which seems to be quite common, is not a condition of only old people. As you can see here, people which are between 50 and 55, there is a fairly high prevalence of congestive heart failure in these individuals. And the second point that I was making earlier, is that the prevalence has increased tremendously during the last ten years. It has more than doubled.

And the reason for that is because we are so successful in treating people who have had several heart attacks. And we fix them, but unfortunately we cannot restore the damage to the heart muscle which has occurred during the heart attack. And eventually they develop this heart failure, which does not kill them immediately, and they go on living for 20, 25 years with this condition, which is extraordinarily debilitating.

So it is a real public health problem, which everybody sees increasing. And again, I don't want to give you the impression that nothing is being done. A lot has been done to treat these patients in a palliative manner so that they don't die within one year or two years and so that we can reduce the number of hospitalizations. But we don't cure this patient.

The good news is that there is an awful lot of research at the cellular and molecular level which eventually is going to help us to take care of these patients in a more effective manner. The ultimate treatment which is used today is heart transplantation. All the cases of heart transplantation that we hear about which are done in this country are made in patients who have congestive heart failure.

The issue is that the demand, the number of recipients or potential recipients far exceed, by orders of magnitude, the number of hearts which are available in the country. So, therefore, we cannot rely exclusively on heart transplantation to take care of these patients.

There is another area of research, which is developing what is called xenotransplantation, that is to use hearts of another species

and to transplant them into human beings. There is some very significant success going on along these lines. But, unfortunately, that is not useful right now.

Mr. PORTER. All heart failure is not congestive heart failure necessarily?

Dr. LENFANT. Well, yes——

Mr. PORTER. Congestive says to me it has something to do with your lungs.

Dr. LENFANT. No, no, no.

Mr. PORTER. No?

Dr. LENFANT. Nearly all heart failures are congestive. Because in many of these patients you have accumulations of fluid eventually in their lungs, usually they have accumulations of fluid in their legs. And definitely you must have heard of people who have swollen legs, fluid in their legs. Most of the time, it is a sign of some degree of congestive heart failure.

Mr. PORTER. My mother died of congestive heart failure about a year and a half ago at age 90, and had these kinds of symptoms, yes.

Dr. LENFANT. But she probably had it for 30 years.

Mr. PORTER. Yes, I suspect she did.

Dr. LENFANT. And that's the point that I'm trying to make. It is not a disease that occurs only in old people. It occurs in people who are in the prime of their life, 50, 55, and have a tremendous potential ahead of them. But this disease, I am sure you have seen with your mother, handicaps people tremendously.

Mr. PORTER. Now, is the congestive part a cause of the heart failure, or is it a result of the heart being too weak to clear——

Dr. LENFANT. It's both what you are saying, the fact is that the blood flow, if you want, is not functioning as it should, and that results in an accumulation of fluid in the tissues, and that's the congestive part of it.

Mr. PORTER. I'm getting a medical education here.

But it's both true that it is not a disease just of old people, but it is true that the prevalence of the disease increases with age, and that since we are a population that is living longer and being healthier in other ways, enabling us to live longer, we are more and more likely to die of this kind of disease in the end.

Dr. LENFANT. That's right.

Mr. PORTER. When your heart weakens, you don't get cancer or have some other cause, your heart simply weakens and you can't——

Dr. LENFANT. That is correct. You see, if you look at these charts, we are starting at 35, 40 years of age here. Some people are beginning at 45, say, to develop congestive heart failure. Because before that, they may have had 10 years or 15 years of high blood pressure, which was not effectively treated or controlled. Or they may have had one or two heart attacks, and that has caused a weakening of the heart. And then with time, that process of congestive heart failure develops.

Mr. PORTER. If you have a heart condition and you're short of breath, and I've forgotten what it's called, but your heart doesn't get sufficient oxygen, is that something that damages the heart?

Dr. LENFANT. Eventually. I mean, many of these patients will have heart failure, due to shortness of breath.

Mr. PORTER. She had that, yes.

Dr. LENFANT. It's a perfectly appropriate term. And the shortness of breath in fact is a compounding factor in the sense that it limits the oxygen, the entry of oxygen into the blood, and that complicates the issue a great deal.

Mr. PORTER. They had her on oxygen for a couple of years, because she was short of oxygen in her blood, presumably, and that would then otherwise damage the heart.

Dr. LENFANT. That is correct. There is a problem with being on oxygen all the time. I mean, the issue of being on oxygen all the time is in itself a problem of some sort, because our system, our whole being, if you want, is used to being in the fraction of oxygen in the air that we breathe. And it is well known that if you have a prolonged exposure to an increased amount of oxygen, as is done in this case, that may cause some complication itself. It is very complex issue.

Mr. PORTER. We'll get back to the larger issues of funding the Institute on our next round.

Mr. Miller.

DIGITALIS

Mr. MILLER. I just have two quick questions, and I'll be interested in your following questions, Mr. Chairman. In your comments you were talking about how digitalis has been used since the 17th century?

Dr. LENFANT. That's correct, yes.

Mr. MILLER. That's a long time ago.

Dr. LENFANT. It's one of the oldest drugs. But would you believe, Mr. Miller, that never before this study were clinical trials done to evaluate its effectiveness.

HEMOPHILIA

Mr. MILLER. The 17th century, that's intriguing.

My question is actually a similar question to one I asked last year when you were here, all of us have a special area of interest, and mine is hemophilia. I don't know if there's anything, last year I don't believe there was much happening in this area. Is there much else?

Dr. LENFANT. There is. And I'm so pleased you are here.

Mr. MILLER. If I was here, you knew that question was coming up.

Dr. LENFANT. Absolutely. And there is something new that has been accomplished this year. I don't know if last year I mentioned to you that we had an animal model of hemophilia, which is a dog animal model. This year it has been developed in a mouse animal model.

Now, I myself asked the question, well, we had a dog, now we have a mouse, so what. The extreme importance of having the mouse is that it's going to speed up the development of treatment and of testing the possibility of gene therapy. Because mice can be bred in a much quicker way, and with more chances of adjustment in the breeding of these animals. And that in effect gives you a

much, much better animal model to test the efficacy of what you can do with that, to explore treatment of hemophilia.

Mr. MILLER. I think it was at the University of North Carolina, a Dr. Brinkhouse?

Dr. LENFANT. He is the one who——

Mr. MILLER. A long time ago.

Dr. LENFANT. Yes, the dog——

Mr. MILLER. He's still working with dogs, after all these years?

Dr. LENFANT. Yes. The mouse also comes from the University of North Carolina, where they have a very active hemophilia program.

If I may say something about, you know about Dr. Brinkhouse and the University of North Carolina——

Mr. MILLER. He's quite up in years, isn't he?

Dr. LENFANT. He is 80 years old, and he still goes to his lab. And you may be interested that his grant, in our Institute, is the oldest grant it has had. And in fact, he has had it for more than 50 years. And it has been consistently renewed.

Mr. MILLER. At one time he was having problems, because he had one strain of dogs, which causes a lot of inbreeding problems and all that. I remember reading that.

Dr. LENFANT. That is correct. But you see, the advent of the mouse model is going to solve many of these problems, as well as speed up the——

Mr. MILLER. Well, did NIH grants help in this development?

Dr. LENFANT. Oh, absolutely. All that is NIH supported work.

Mr. MILLER. Well, great. Great.

Dr. LENFANT. Dr. Brinkhouse and Dr. Harold Roberts are our two champions in the hemophilia business.

Mr. MILLER. Yes, I'm familiar with them a little bit.

Dr. LENFANT. As I was reading, actually, expecting to see you here, I was reading the testimony from last year. And Dr. Varmus, during his questioning last year, pointed out to you that biotech companies also are working quite hard on the issue of hemophilia.

The reason is that many people who are interested in gene therapy will tell you that one of the diseases, if not the disease, where gene therapy actually will work first, and best, is hemophilia. It may be debatable, I'm sure that perhaps Dr. Varmus may have another idea. But that's what lots of people are saying.

And for that reason, biotech——

Mr. MILLER. Of course, it may take several years, a long time, too.

Dr. LENFANT. Yes. For that reason, the biotech companies are working very actively in this area. And, although I don't know what, we hear through the grapevine that there may be some very interesting findings coming from the biotech area.

Mr. MILLER. Yes, I think the Genome Project is one spinoff in that area. Is that right?

Dr. VARMUS. Well, most of the relevant genes have been cloned already. Now the problem is making the products or finding some way to deliver the correct forms of the gene to the patient.

Mr. MILLER. To go from the basic to the applied, in a word.

Thank you. Thank you, Mr. Chairman.

CARDIOVASCULAR DEATH RATES

Mr. PORTER. Thank you, Mr. Miller.

Dr. Lenfant, going back to cardiovascular deaths, we learned earlier this year that cardiovascular deaths had increased in 1993 for the first time in many years. What should we make of this? Is it unexpected, or is it a fairly predictable consequence of demographic changes?

Dr. LENFANT. Well, it's a methodological artifact. All the death rates that I'm reporting to you, and are continuously reported, are what we call age-adjusted. That is, we adjust for changes in age of the population. So if you want, the curve that we are giving you, is as if the age distribution of the population remained the same. That's what we call age-adjusted.

The data which came out earlier this year which showed an increase were not age-adjusted, and therefore are not comparable to what you have seen. We have used these data which were produced a few months ago, and we age-adjusted them. And what it shows is a flattening, not an upturn.

What's going to happen? I can't predict, except that in my personal opinion, I think we are going to see a continuation of the decline for some years. But we have to recognize that sooner or later, that decline is going to flatten.

SLEEP DISORDERS RESEARCH

Mr. PORTER. As you know, I've long had an interest in sleep disorders, and the sleep disorders research center that you support. You indicated to the sleep disorders advisory board last month that NHLBI spent almost \$2 million less than projected in 1995 on sleep disorders research, because of a lack of applications.

You also indicated that you had to drop below the usual pay line in order to fund the amount of sleep research that you did. Have you developed any strategies to encourage more applications from the sleep research community?

Dr. LENFANT. Yes. First of all, Mr. Chairman, you do recall that Congress requested that the Sleep Center and the institutes and Dr. Varmus develop a research plan for research on sleep disorders. That plan has been developed and approved by Dr. Varmus, and is now being widely disseminated and distributed.

I have made some arrangements so that it will be published in a number of scientific journals. And I think that is going to stimulate a great deal of research. Because it happens all the time, when scientists see a plan which is logical, makes sense, they become interested in it and devote some of their effort to answering the questions which are posed.

So I think that it is going to have a very significant impact. Probably not in the next year, but within two or three years, we are going to see an upsurge in this number of applications. But the fact remains that so far, we do not see an increase in the number of applications, and that is the reason why I made that statement.

The second part of the statement is that many of the applications that we are seeing are not competitive with research grant applications in other areas. While we have discussed that with our National Advisory Council, and it has agreed that in some instances,

some of these applications which are more at the margin should be paid in order to help stimulate the field.

But it is not something that we can do to a great extent. Because it can be unfair to those applicants who are coming with better applications in other areas that we serve. So I'm quite confident that that is going to change.

Mr. PORTER. The advisory board has drafted two Requests for Applications in molecular biology and the genetics of sleep. Do you plan to publish these RFAs? Do you think there will be a good response to the RFAs from the outside researchers, given the trouble you have had so far in getting quality applications?

Dr. LENFANT. These are being worked out at the present time. What the Board did was not to develop an RFA, but to make some suggestions as to how an RFA could look. So the work to develop the RFA is ongoing. It is my expectation we will present these RFAs to our National Advisory Council in early June. And if the Council, concurs with that, then we will issue these RFAs.

HEART TRANSPLANTS

Mr. PORTER. You mentioned xenotransplantation. And as your testimony describes, one of the research ideas being pursued is the development of transgenic pig hearts to be transplanted into humans. Advocates of this type of research cite the continuing shortage of human organs for transplantation. Opponents cite the fear of spreading animal diseases to humans through transplants. Do you think the benefits outweigh the risks?

Dr. LENFANT. Oh, absolutely. Absolutely. First of all, the pigs, in this case, which are used for genetic manipulation or adaptation to this situation, are very carefully selected. These are not pigs coming from any farm in the country. They are bred under some very special circumstances, where the risks of these pigs having bacteria from unknown conditions is extremely limited, extremely limited.

So I think the potential of this approach is quite significant and important. My personal opinion on that is that within some period of time, the biology of that is going to be quite effective. It is not that easy to make a pig whose heart can be put in a human being without rejection. I mean, that requires a huge amount of work and to understand the biology. That will be resolved.

But I think that from what we are hearing, there will be a number of sociological and ethical issues and spiritual issues which are going to have to be addressed.

Mr. PORTER. In other words, at some point we'll be able to make genetically a pig whose heart is very close to a human heart, or closer than they are now?

Dr. LENFANT. Well, no, not closer. What it does is that through genetic manipulation, you suppress the proteins which result in that heart being rejected by the human. It's really a pig heart, but you can put it in a human by having eliminated the risk of rejection.

Mr. PORTER. There's no way that you can genetically manipulate the pig in such a way that the heart becomes more similar to a human heart?

Dr. LENFANT. To start with——

Mr. PORTER. It's already very similar?

Dr. LENFANT. It so happens that the pig's heart——

Mr. PORTER. Is already——

Dr. LENFANT. It's quite comparable to that of the human. That's why the pig has been selected for this work.

CHOLESTEROL SCREENING

Mr. PORTER. The American College of Physicians recently published guidelines on cholesterol screening that contradict the guidelines developed by your Institute in 1993. They propose screening beginning at a later age and ending earlier in the life cycle.

Has your Institute responded to the ACP recommendations? Do you expect other major health groups to endorse the ACP guidelines?

Dr. LENFANT. Well, that is a very, very interesting issue. First of all, I'm sure that's not going to surprise you, Mr. Chairman, the Institute does not agree with what the College of Physicians has said. And let me give you a very simple example. One of the arguments to start screening when you are 40 or 45 is that the risk of heart attack is very low in younger people. And we all agree with that. There is no dispute with this point.

However, if a young person has a high cholesterol, we know from very solid data that that person is prone to develop a heart attack when he or she will be 40. [CLERK'S NOTE.—Subsequent to the hearing, NHLBI changed this age to 50 for the record.] And therefore, to me, it is inconceivable that you do not give that person the opportunity to know what he or she risks 10 years later. [CLERK'S NOTE.—Subsequent to the hearing, NHLBI changed this to say "30 years later" for the record.]

And I personally would want to know if my cholesterol was high, and I do know, so that I can do something about it. At least I have that choice. And I don't think that we should deny the public a choice that the public can make about its health.

And now, I don't know whether there will be some other groups coming up with the same thing. One thing that I can tell you, I just heard this morning before I came here that the Association of State and Territorial Directors of Health Promotion and Public Health Education in the United States, which is a very large association of public health officials, is going to give the National Cholesterol Education Program an award during their convention a couple of months from now for this program. So what I'm saying here is that there are lots of people who think that our program is valuable and important, and has a great potential in terms of prevention of cardiovascular disease.

AIDS RESEARCH

Mr. PORTER. One of the recommendations of the Levine panel reviewing the NIH AIDS research portfolio was to establish more precise definitions to classify an institute's research as AIDS or non-AIDS. One example the panel cited was the categorization of artificial blood products research as AIDS related. How does your Institute determine what types of research are classified as AIDS related, and do you plan to review the designation process?

Dr. LENFANT. The answer to the latter question is yes, and in fact, I have to say that we do not disagree with this recommenda-

tion of the Levine panel. Because it is done today. Had that same recommendation been made years ago, we would have strongly disagreed.

In fact, that's why we initiated this program on the blood substitutes. In those days, the way we could check for safety of blood, to detect a carrier of viruses, and the risk was one per approximately 40,000 or 50,000 transfusions. Today because of the progress that has been made to detect contaminants, the risk is one per 400,000 transfusions.

I can assure you, I'm not aware of anyone receiving 400,000 transfusions. And so therefore, the risk is very small. And for that reason, that recommendation is quite appropriate.

Now, regarding the bigger side of your question, what are we going to do in the future? As Dr. Varmus explained yesterday, he has met with some Institute Directors, and I was part of this meeting, and we are undertaking a process to better identify what is going to be classified as AIDS research.

I think that we all agree that there is AIDS research which, if you want, is working on the viruses which are responsible for the condition. But if you move away from that, there is a type of research which perhaps is related to this research, and I think that kind of research can be included. Because eventually it will be very important to these problems.

But I think what I'm trying to say is that I think we have to be very guarded against a definition which is either black or white. There is an area in between. I don't know if Dr. Varmus will agree with me, but that's my opinion.

SERVICE CENTERS

Mr. PORTER. You're one of the two institutes that have established service centers to assist other institutes with technology transfer initiatives. Which institutes have signed up as your customers, and how does this arrangement work? Have you been able to quantify the savings to NIH as a whole from the development of these service centers?

Dr. LENFANT. Well, I know at least of one which is, where we have made an assessment of the savings. And that is in procurement. Our Institute is a service center for procurement for a number of other institutes. And the marriage, correct me if I'm wrong, but I think that our costs, which they pay, is approximately \$50,000. And the savings to this institute are approximately \$400,000. Is that correct?

Mr. WEHLING. A little high. The savings are about \$100,000.

Dr. LENFANT. Basically, we're doing it, it costs half of what it was costing if they were doing it. We are in the process of getting more and more clients. I understand that Dr. Varmus's office has contacted us to provide service to him. And we'll send a bill there. [Laughter.]

Dr. VARMUS. We'll pay it.

CORD BLOOD STEM CELLS

Mr. PORTER. I called them customers, they're really clients.

Stem cell transplants seem to hold promise in the future as an alternative to bone marrow transplants. How are stem cells ob-

tained and harvested? Would this research be affected if the use of fetal tissue in research were revisited?

Dr. LENFANT. There are two kinds of stem cells, or two sites to harvest stem cells. One is to take it in the blood; that's very laborious and the payoff is not good at all. The second way to harvest stem cells is from the umbilical cord between the placenta and the newborn at the time of delivery. That has nothing to do with fetal research, it's just at the time of normal delivery, you collect the blood from the cord. And in fact, I believe that I mentioned last year that the Institute was initiating a very substantial program to assist this effort.

Let me tell you, Mr. Chairman, the prospect from cord blood transplants, cord blood cell transplants, are just enormous. The potential that we have with that is so significant that it is the reason why the Institute has devoted so much of its resources to this program, because of the potential.

Let me just give you an example. Today, no one would think of doing bone marrow transplantation for the treatment of a patient with sickle cell disease or thalassemia, or other similar blood disorders.

However, some work is ongoing already which has demonstrated that by using cord blood cell transplantation, you have some very positive results and significant survival. The reason for it is that the immunogenicity, that is, the reaction to the cord blood cells, is very low, if any, in contrast with that from bone marrow, which can be very high.

Because it is so difficult to have a perfect matching with an unrelated donor, nobody wants to take the risk of a rejection in a patient that has this disease, whereby doing a transplantation using cord blood cells, you don't have that risk. So there is an area of enormous potential.

Mr. PORTER. Do you have such a thing as stem cell blood banks?

Dr. LENFANT. Yes. Yes, we have performed, supported, I should say, a demonstration project that's a blood bank in New York where they have accumulated approximately 5,000 specimens which are banked there. And that is what is being used for the work which is ongoing.

What the Institute is doing is developing a network for the collection of these cord blood cells, and we are in the process of initiating that, as well as selecting a number of transplant centers, which will be using these.

Mr. PORTER. So the problem, as I understand it, with bone marrow, has always been finding the match, so that you don't get rejection.

Dr. LENFANT. Especially in African-Americans, very difficult.

Mr. PORTER. So with stem cells, you don't have to worry about that nearly as much, is that correct?

Dr. LENFANT. Cord stem cells.

Mr. PORTER. Cord stem cells.

Dr. LENFANT. That is correct. I mean, that's what this demonstration project using a network is going to establish. But today, the working hypothesis is that yes, we don't have to worry about it.

Mr. PORTER. Can you use cord stem cells to treat cancer patients?

Dr. LENFANT. Eventually. I must admit I am not familiar with what's going on in this area. But I do know that that has been proposed for the treatment of breast cancer, for example. For blood cancer, the answer is yes. But for other cancers, such as breast cancer, that has been discussed.

But there have been lots of problems, due to the matching. And if what we believe is going to happen turns true, then if the fact that a transplantation of new cells, new blood cells, in these cancer patients will help them, that would do it.

NATIONAL MARROW DONOR REGISTRY

Mr. PORTER. If I read what you're saying correctly, we have some funds that go into encouraging the bone marrow registry, yes, a registry, so that, it would be too early to say that that can be replaced. We have to see whether—

Dr. LENFANT. That is correct.

Mr. PORTER. Yes.

Dr. LENFANT. You may recall, Mr. Chairman, that the Institute was actually responsible for that registry, and it was transferred to the Health Resources and Services Administration last year.

Mr. PORTER. Yes, right.

Dr. LENFANT. Two years ago. And that is true. If the cord blood stem cell project is positive and successful, eventually that would replace that registry.

Mr. PORTER. Mr. Young of Florida, who is the Chairman of the Defense Appropriations Subcommittee, and is not often with us, because of his other major assignment, is very, very interested in this area, and I'll pass along what I've learned today to him. But it's certainly too early to back off from that.

Dr. LENFANT. Oh, absolutely. In fact, it would be a terrible mistake to back off from that at this point in time. Because every day we hear of additional needs for the registry.

MODULAR GRANTS

Mr. PORTER. Your Institute has experimented with the modular grant concept, providing funding by \$50,000 increments up to \$200,000. This system relieves the applicant of the burden of presenting detailed budget information because of the standard size awards. What has been your experience with the modular grant concept?

Dr. LENFANT. Everybody loves it. It's not very often that everybody loves what the Government does. But in this case, everybody loves it. The grantee loves it, their institutions love it, we love it, and it really, it really makes the process so much easier. And there is no nickel and diming, and once the thing is in, you know exactly how it's going to work.

And really, people are very happy. I think Dr. Varmus also thinks it's good and actually has required that the Division of Research Grants adopt the system for some of the unsolicited grants. We started it as a demonstration, with solicited grants.

Dr. VARMUS. It's a policy to be taken up by the institutes which actually fund the grants, but I've been advocating for this for some

time. And the very important pilots that were done in the Heart, Lung and Blood Institute have helped to assure us that this is a good mechanism. It won't replace requests for specific amounts of funds by any means, but it will be developed into a more widespread tool.

FOLIC ACID

Mr. PORTER. Now, I have a series of shorter questions, as we finish up. And I'll try to ask them quickly.

We know folic acid's role in preventing birth defects. But now we understand that it also appears to help prevent heart disease. What is the research base for this conclusion? Taking folic acid or eating foods fortified with folic acid would seem to be a simple fix. Do you expect this to be recommended as a public health measure?

Dr. LENFANT. Well, that has been done, as you know, Mr. Chairman. The decision has been made by the Secretary to initiate a food fortification program with folic acid. I must say, that throws a bit of a monkey wrench in our own thinking. Because we were in the process of developing a clinical trial.

All that we know relative to cardiovascular disease is the result of observational studies. A clinical trial is where we compare two regimens, one with and one without. We are now readjusting our plans and seeing how we could develop such a study now that this fortification program has been initiated. But it is a critical issue that must be addressed.

CALCIUM CHANNEL BLOCKERS

Mr. PORTER. Last fall, there was an outcry about calcium channel blocker drugs and their link to heart disorders. Your Institute issued a warning about certain types of these drugs. Some of the drug manufacturers are contesting your recommendations. Where does this agreement stand at the moment, Dr. Lenfant?

Dr. LENFANT. Well, I am surprised to hear that some are contesting our recommendations. Because, to my knowledge, all the drug companies which are producing the calcium blockers for which we raised questions are now initiating themselves clinical trials, to demonstrate whether or not the issue is real. And in effect, that complicates our own programs. Because we ourselves have initiated, two or three years ago, a program to evaluate the issue.

Our statement was one of caution. It was not one of rejection. And only with one calcium blocker, the fast acting one, as opposed to the slow acting one.

ATHEROSCLEROSIS

Mr. PORTER. A February article in the Journal of NIH Research indicates that atherosclerosis is linked to the presence of infectious bacteria. Does this have implications for treatment similar to those for ulcers, which have been found to have a bacterial origin?

Dr. LENFANT. The answer is yes. If you can identify the bacteria in question, which is, chlamydia pneumonia, I believe. And the prevalence of this cause for atherosclerosis is very low. It is not a huge problem. I mean, clearly, the dominant cause of atherosclerosis

sis is lipid excess in the blood. But the answer to your question is yes. If it is identified, it can be and should be treated.

CMV AND ANGIOPLASTY

Mr. PORTER. The Washington Post reported in February that some of your researchers had found that the failure of angioplasty within the first six months may be related to the presence of the CMV virus. Does this suggest a therapy that could prevent the re-clogging of arteries which occurs in about half of the angioplasties?

Dr. LENFANT. Yes. Yes, Mr. Chairman. That's a very interesting observation. It comes from laboratory work where the virus was identified. But also from observational epidemiological studies where, looking at people who have an angioplasty and within six months the obstruction reoccurs, because of proliferation of smooth muscles in that artery. And that proliferation may be triggered by the presence of this virus.

And it has been found that indeed, this reoccurrence of the obstruction is more frequent in people who have had at one time or another an exposure to CMV. So it is a very interesting avenue, and there is an awful lot of work which is going on in our laboratories on this problem.

ASTHMA NETWORK

Mr. PORTER. Tell us more about the asthma clinical research network that you have established. Is its principal purpose the testing of drugs to treat asthma?

Dr. LENFANT. Well, the principal, the main purpose of it is to identify the best possible therapy for these patients, not really just the testing of a drug. Having said that, because of the importance of asthma and the huge interest of the pharmacological industry, they produce new drugs, and some of them are indeed tried out in this network.

The issue, Mr. Chairman, if I may say so, is that asthma is a condition from which nobody should die if it is properly treated. And the purpose of this network is to try to identify the best possible treatment on the basis of the clinical manifestations of the patient. And that of course involves the utilization of new drugs which are appearing on the market.

LAM

Mr. PORTER. There seems to be increasing interest among Members of Congress in lymphangioleiomyomatosis. I thought I'd try that, just to see if I could do it. [Laughter.]

Dr. LENFANT. For short it's called LAM.

Mr. PORTER. LAM. We are pleased that your Institute has a program announcement out on the disease. The committee has been approached about encouraging you to start an LAM disease registry. What are the most productive approaches to funding LAM research at this stage of its development?

Dr. LENFANT. Well, there are two avenues which are pursued by the Institute. One is indeed to have a registry, because it is such a rare disease. And by having a registry, we know where these patients are, and therefore it makes it easier to study them. You can

study a disease only to the extent that you have the patients. And the registry would give us the opportunity of having the patients.

And the second avenue is to look at the disease at the cellular and molecular level from tissue which is from these patients. Unfortunately, all die from it. And so there is a tissue bank which is being developed.

And I would say that in all the laboratories in the country the Institute is really the leader in the world in the study of this condition at the present time. The chief of our program has reoriented his activities to study this condition at the molecular level. It will be a tough problem to solve.

Mr. PORTER. Dr. Lenfant, you've answered all of Mr. Miller's questions, you've answered every one of my questions. We are on time. The answers have been outstanding. Your testimony was excellent. Maybe I'll conduct these meetings in the future without the subcommittee and I can get through all my questions. [Laughter.]

I don't think I've ever gotten through all my questions before. So we very much appreciate your testimony this morning, and the fine job that you're doing at the Institute, and the very candid and straightforward way you answer our questions.

Thank you so much for being here.

Dr. LENFANT. Thank you.

Mr. PORTER. The subcommittee will stand in recess for five minutes.

[The following questions were submitted to be answered for the record:]

SELECTED AREAS OF RESEARCH

Mr. Porter: Identify 1995-1997 spending on asthma, sickle cell disease, cystic fibrosis, Cooley's anemia, transfusion medicine, tuberculosis, hemophilia, hypertension, sleep disorders, LAM, and cardiovascular disease.

Dr. Lenfant: NHLBI funding estimates for these research areas are shown on the table below.

	1995	1996	1997
	<u>Actual</u>	<u>Estimate</u>	<u>Estimate</u>
Asthma	\$47,735,000	\$49,250,000	\$50,100,000
Sickle Cell Disease	46,355,000	47,800,000	48,600,000
Cystic Fibrosis	15,969,000	16,500,000	16,800,000
Cooley's Anemia	14,197,000	14,650,000	14,900,000
Transfusion Medicine	42,039,000	43,400,000	44,200,000
Tuberculosis	11,393,000	11,750,000	11,950,000
Hemophilia	17,097,000	17,875,000	18,125,000
Hypertension	121,727,000	125,550,000	127,700,000
Sleep Disorders	13,674,000	14,250,000	14,500,000
Lymphangioleiomyomatosis (LAM)	0	800,000	825,000
Cardiovascular Disease	783,673,000	823,123,000	838,614,000

The Institute will make a special effort to find new investigator initiated grants that propose research on sleep disorders. If NHLBI receives such applications, we will endeavor to obligate more for sleep related research than the \$14,500,000 currently estimated.

RESEARCH CENTERS

Mr. Porter: Identify the number and subject matter of research centers supported in 1996.

Dr. Lenfant: In 1996 the National Heart, Lung and Blood Institute plans to support 75 research centers as shown below:

<u>Title</u>	<u>Number of Centers</u>
Molecular Genetics of Hypertension	6
Arteriosclerosis	7
Ischemic Heart Disease, Sudden Cardiac Death, and Heart Failure	10
Ischemic Heart Disease in Blacks	2
Pediatric Cardiovascular Disease	3
Chronic Diseases of the Airways	4
Occupational and Immunologic Lung Diseases	4
Lung Biology and Disease in Infants and Children	7
Cystic Fibrosis	4
Cardiopulmonary Disorders during Sleep	3
Acute Lung Injury	6
Hematopoietic Stem Cell Biology	3
Hemostatic and Thrombotic Disease	3
Transfusion Biology and Medicine	3
Comprehensive Sickle Cell Centers	<u>10</u>
TOTAL	75

NATIONAL CENTER ON SLEEP DISORDERS RESEARCH

Mr. Porter: There is some concern among the sleep research community that the National Center on Sleep Disorders Research is not receiving adequate funding and that the funding levels cited as Center funding include many projects that NHLBI would have been supporting regardless of the establishment of the Center. Their contention is that the Center's budget is actually much lower than reported. How do you respond to this concern?

Dr. Lenfant: In FY 1995 the National Center on Sleep Disorders Research (NCSDR), as part of the National Heart, Lung and Blood Institute (NHLBI), supported \$13.7 million in sleep disorders research. The FY 1996 and 1997 targets are approximately \$14.3 and \$14.5 million respectively. Sleep related research across the NIH, as reported by each Institute, totals \$72.8 million in FY 1995, \$76.4 million in FY 1996, and \$78.3 million in FY 1997.

The NCSDR has worked effectively with other NIH Institutes to stimulate more research through joint activities. The creation of the NCSDR has provided greater attention and increased funding of sleep research throughout NIH, leading to significant growth in the field, which may not have occurred without the NCSDR. In addition, the National Sleep Disorders Research Plan is now complete and is receiving wide distribution within the research community. The Plan is expected to draw attention to the scientific questions that need to be answered, and the NCSDR anticipates that the number of high quality, investigator-initiated research grant applications will increase. As this growth occurs, the NCSDR will fund some of these applications, while others will be supported by the Institutes to which they are assigned.

Mr. Porter: Another concern of the sleep community is that the Center's director only works one-third of his time for the Center and that this is seriously impairing his ability to carry out the mission and goals of the Center. How can this be remedied?

Dr. Lenfant: Currently, there is a permanent part-time Director for the NCSDR. Although the work of the Center is growing, at present there is no indication that the goals, mission or programs are impaired or suffering from lack of adequate attention. On the contrary, it appears that most, if not all, aspects of the Center are being handled quite adequately under the present arrangement. Given the current workload of the NCSDR it would appear that the current part-time position is appropriate. However, as the programs, activities and management needs of the Center increase, we will consider increasing the amount of time of the current Director to the NCSDR, or possibly recruit a full time Director if the workload demands it.

BLOOD STEM CELL

Mr. Stokes: A lot of attention is being given to blood stem cell research in the development of new treatments. For which diseases does this research offer the most promise and why?

Dr. Lenfant: The success of marrow transplantation for the correction of a wide variety of acquired and genetic blood-related disorders has focused attention on the hematopoietic stem cell as a potential substitute for marrow and a possible target for gene therapy. Use of the stem cell for transplantation and gene therapy holds particular promise for patients with leukemia, aplastic anemia, sickle cell anemia, Cooley's anemia, Fanconi anemia, and several others rare diseases. The stem cell is an ideal cell for transplantation and as a target cell for gene therapy because this cell is not only capable of self-renewing for the life of the patient, but is also the source for all blood cells and therefore capable of forming all the other blood cells such as red cells, platelets, and white cells.

Mr. Stokes: How much is included in the FY 1997 budget for this activity?

Dr. Lenfant: The FY 1997 estimate for blood stem cell research is \$27,500,000.

MINORITY HEALTH

Mr. Stokes: Where do we stand today with respect to closing the gap in minority health with respect to the diseases and disorders that are under the purview of your Institute? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Lenfant: The established risk factors for cardiovascular disease (CVD) that are known to affect minority groups more severely or extensively than whites are high blood pressure (especially African Americans) and diabetes. A common underlying cause of both of these conditions is obesity, which is more prevalent in several major minority populations (African Americans, especially women, Mexican Americans, southwestern Indians, and Pacific Islanders). An understanding of the causes and course of obesity in adolescent African American and Caucasian girls will soon be available from the Institute's Growth and Health Study to help guide prevention efforts. A separate obesity prevention study of Indian school-children, called Pathways, is about to conclude its pilot phase. With regard to effects of other aspects of diet

on high blood pressure, the Dietary Approaches to Stop Hypertension clinical trial, with two-thirds of the participants from minority groups, will conclude later this year. As far as treatment and control of established high blood pressure is concerned, levels are similar in African Americans and whites, but worse in Mexican Americans, and African Americans still have more complications of hypertension, such as stroke, than other groups. In response, five grants were funded three years ago under an NHLBI initiative entitled Improving Hypertension Care For Inner City Minorities. Also, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial of 40,000 patients will have about one half African Americans; the nearly 6,000 minority patients already enrolled represent the largest such group ever studied in a clinical trial of CVD treatment.

Since 1971-74, there has been no narrowing of the black/white gap in proportion of persons with hypertension; prevalence rates are still about one and one-half times higher in blacks than whites. In contrast, proportions of persons who have high cholesterol levels, or who smoke cigarettes, have been declining, a little faster in blacks than whites and more for women than men. Whites have had greater increases in the proportion of obese persons over time than blacks. The gap between Mexican-Americans and whites in the prevalence of obesity has also narrowed.

The black/white gap in rates of cardiovascular surgery, specifically catheterizations, angioplasty and coronary bypass surgery (CABG), remain very large. For example, the rate of bypass operations in whites in 1993 was 3.6 times the rate in blacks; for angioplasty 2.4 times and for catheterizations 1.48 times. There has been a modest narrowing of this gap in treatment since 1990.

In both men and women, percent declines in age-adjusted death rates for heart disease between 1985 and 1992 exceeded 17 percent in nonhispanic whites but ranged from only 5-16% in blacks, American Indians, Asian-Pacific Islanders, and Hispanics. For stroke, percent declines exceeded 15% in nonhispanic whites, were even a little steeper in black women and Hispanic men, but were very modest for the other populations. Thus, gaps in mortality between the minority and white populations widened for these two causes of death.

While there has been a very large decline in the infant mortality rate for neonatal respiratory distress syndrome in both white and black infants, the rate was 1.7 times higher in blacks than whites in 1983 and three times higher in blacks by 1993, an appreciable widening of the gap. In 1983, the proportion of persons under age 45 with asthma was 4.7% in blacks and 3.9% in whites. By 1994, asthma prevalence increased, but the black/white difference had almost disappeared: 5.8% in whites and 5.9% in blacks. For asthma, death rates under age 24 are about five times higher in blacks than whites with no sign of narrowing over the 1980 to 1992 period.

In summary, the gaps in cardiovascular and pulmonary health between whites and minorities are improving for risk factors, surgery, and asthma prevalence and widening for mortality, with the exception of congestive heart failure. It is important to note that the data cited here are subject to year-to-year fluctuations that complicate the exact determination of changes for whites relative to changes for the minorities.

ASTHMA

Mr. Stokes: According to your opening statement, asthma death rates are increasing. What major initiatives are underway to address this critical health problem?

Dr. Lenfant: The NHLBI has initiated several major programs directed at the critical problem of increasing mortality from asthma.

A major contributor to asthma mortality is the delay in seeking appropriate care during serious attacks. Projects supported by NHLBI are seeking to identify the risk factors for the sudden, life-threatening attacks, and find explanations for the patient's inability to perceive the seriousness of the attack. In addition, new strategies are being developed for educating patients who seek routine care only in the emergency room, on how to better manage their asthma and prevent emergencies. The NHLBI invests in developing and testing new treatment modalities. For example, the Childhood Asthma Management Program, is comparing, in over 1,000 children with asthma, the effectiveness of three different treatments. An ancillary study is looking into the effects of air pollution on asthma severity. The NHLBI Asthma Clinical Research Network, is developing and evaluating new treatments as well as exploring optimal ways to use currently existing therapies.

Environmental and economic factors including inadequate access to health care are believed to contribute to the higher asthma-related death rates in minorities. NHLBI is supporting research on the factors, including indoor and outdoor allergens and pollution, contributing to asthma in minorities. The essential goal is to develop appropriate intervention programs.

The NHLBI is also engaged in developing programs that translate research findings into clinical practice and help decrease deaths from asthma through the National Asthma Education and Prevention Program (NAEPP). These efforts include developing and updating guidelines for asthma management, designing continuing education activities targeted to different care givers, and plans to reach out to patients, families and communities through print, radio and other mass media.

Mr. Stokes: Doctor, asthma ranks second among the chronic health problems most frequently reported by African Americans, especially those under 18 years of age. Would you bring us up-to-date on programs underway at the Institute that are designed to address this serious health problem in at-risk populations?

Dr. Lenfant: The NHLBI is addressing the problem of increasing prevalence of asthma in minorities through research, training, educational and other interventions.

Specific research topics include the effects of exposure to environmental tobacco smoke on asthma severity in African American and Hispanic children; ways to link those who frequently use emergency services with primary care providers; factors that contribute to the development and/or severity of asthma with the goal of designing appropriate interventions that minimize or eliminate the risk factors; and development partnerships between schools, families and care givers to improve communication, management and care of minority children.

Children with asthma miss school twice as much as other children, restrict their physical activities, and have twice the odds of grade failure compared to well children with similar income. To address this problem NHLBI recently initiated a new program on "Interventions to Improve Asthma Management in Schools." All of the institutions in this program have components that focus on inner-city schools. Also, new educational materials (e.g., using videos and computers) for teaching Hispanics and African American families about asthma are being developed and evaluated. A report entitled "Asthma Management in Minority Children: Practical Insights for Clinicians, Researchers and Public Health Planners has been prepared and is being disseminated.

This report provides guidelines to reduce hospitalizations, emergency room visits, and school and work-days missed and is based on results from an NHLBI initiated grant program on Interventions for the Control of Asthma among Black and Hispanic Children.

In research training, the NHLBI asthma academic award program is modifying medical school curriculums for asthma, by incorporating the NHLBI Guidelines developed by the National Asthma Education and Prevention Program in order to improve skills of physicians treating asthma patients.

To build community coalitions to deal with asthma in the African American population; four regional conferences will be held this year in areas experiencing the highest asthma mortality rates. In addition, nationwide media campaigns are currently being targeted to recognize the seriousness of asthma and the importance of seeking prompt medical care.

GENE REPOSITORY

Mr. Stokes: What is the association of genetic predisposition with the diseases and disorders under the purview of your institute?

Dr. Lenfant: Some diseases, such as sickle cell disease, are caused by a defect in a single gene. However, the number of individuals affected by a given single gene disorder are relatively rare. Common, highly prevalent diseases, such as asthma, hypertension, coronary artery disease, stroke, and chronic obstructive pulmonary disease are very complex and difficult to understand, because they are multifactorial - that is, there are numerous genetic factors and a number of environmental factors that interact with each other in complicated ways. In these complex diseases, an alteration in a single gene is generally not sufficient in and of itself to cause the disease. Instead, it provides a genetic susceptibility, which, when combined with other genetic alterations and environmental factors, leads to illness.

The NHLBI is funding a number of special programs to utilize the latest developments in molecular genetics to determine the genetic and non-genetic factors of complex diseases. Examples that focus on specific diseases include the Collaborative Study on the Genetics of Asthma, the Family Blood Pressure Program, and the Family Heart Study. In addition, the Institute has established the Mammalian Genotyping Service, which provides rapid, inexpensive genotyping, which is required for genetic studies. The NHLBI is also establishing a Molecular Genetics Course to help train future investigators who will

utilize the tools, concepts, and methodologies of modern molecular genetics to understand complex heart, lung, and blood diseases.

Mr. Stokes: What can you tell us about the status of the gene repository as it relates to these diseases?

Dr. Lenfant: The NHLBI does not support or maintain a gene repository. Your question may pertain to the National Center for Human Genome Research and its effort to map the human genome. As the Human Genome Project approaches fruition there will be a number of important informational resources. Examples include the Genome Data Base, which includes mapped genes, gene locations, and other map elements, and GenBank, which includes gene sequence information. As soon as genes are discovered and sequenced, the information is deposited in the appropriate database. NHLBI-supported investigators send their data to these repositories, when appropriate, and can use these databases to receive information that will help them in their research efforts to understand heart, lung, and blood diseases.

Mr. Stokes: What can you tell us about the status of the gene repository as it relates to African Americans, and other minorities?

Dr. Lenfant: Genomic databases, such as GenBank and the Genome Data Base, store and make available data from investigators regarding mapped genes, gene locations, other map elements, and gene sequences. NHLBI-supported investigators supply information to such data repositories after it is considered valid and accurate. NHLBI-funded human studies to identify genes involved in heart, lung, and blood diseases include data on women and minorities. These data may prove useful in understanding the role of genetic factors in disease susceptibility an

SICKLE CELL DISEASE

Mr. Stokes: According to the budget justification, children with sickle cell disease are at 100 times greater risk than normal infants and young children for life-threatening pneumococcal infections. I understand that recent results from the Institute's penicillin study offer promise for these children. How much hope does this finding offer children suffering from sickle cell disease and their families?

Dr. Lenfant: The findings from our study to determine the risks of discontinuing penicillin in young children are very significant. Children with sickle cell anemia who have not had a prior severe pneumococcal infection or a splenectomy and are receiving

comprehensive care may safely stop prophylactic penicillin therapy at 5 years of age. At this age, there is less likelihood of overwhelming pneumococcal infection and continuing penicillin may result in the development of penicillin-resistant organisms.

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to how much promise gene therapy and bone marrow transplantation hold for advances in sickle cell disease?

Dr. Lenfant: There are two significant advances that have taken place in the area of gene therapy for sickle cell disease since last year. First, one of the prerequisites for scientific advances in the area of gene therapy is a good animal model for the disease. Mouse models of sickle cell disease have existed for several years. However, these mice have had limited use as a model for gene therapy, because mouse hemoglobin was still present in a significant proportion and reduced the pathological effects of the sickle hemoglobin. Recent advances in "gene knockout" technology have allowed the production of mice with only human sickle hemoglobin. In addition, these mice have the gene for human fetal hemoglobin so that genetic therapies aimed at increasing fetal hemoglobin can also be tested. Second, a human fetus with the X-linked form of severe combined immunodeficiency disease has received a successful *in utero* transfusion of bone marrow stem cells from the father. Bone marrow transplantation *in utero* eliminates many of the problems of rejection and graft versus host disease that occur in transplantations that occur after birth. Bone marrow transplantation *in utero* should be beneficial in ameliorating the effects of sickle cell disease, and further investigations of this preemptive strategy are planned.

The experience in the United States with bone marrow transplantation in individuals with sickle cell anemia is still limited. Currently, an NHLBI-sponsored U.S. collaborative study is underway using a standard protocol in patients where stroke is the major indication for transplantation. Twenty-four patients have been transplanted and twenty-two of them remain alive. Four patients have experienced graft rejections while one patient has remained clinically stable (requiring no transfusions) with a sickle hemoglobin level resembling sickle cell trait. Thus, these very early results suggest that marrow transplantation for young patients with asymptomatic sickle cell anemia could potentially be curative. However, additional studies and long-term follow-up of these patients is extremely important. The continued search to find therapies for the successful treatment/cure of sickle cell anemia is essential to be able to offer these patients the best chance for greater longevity and a better quality of life.

HEART DISEASE IN AFRICAN AMERICANS

Mr. Stokes: Last year's house report included language urging the Institute to strengthen its research in ischemic heart disease in African Americans. What can you tell us this year that you could not tell us last year with respect to this area of research?

Dr. Lenfant: The Institute has several new items to report regarding ischemic heart disease (IHD) in African Americans. Preliminary results from an Institute-funded program, Mechanisms Underlying Ischemic Heart Disease (IHD) in Blacks, have identified a number of physiologic differences, which are more common in African Americans that appear to contribute to the virulence of IHD. Excess hypertension, diabetes and an unfavorable blood lipid component (Lp(a)) have been implicated in contributing to excessive IHD; these risk factors continue to be evaluated in a large group of African American men and women with documented IHD. Other research suggests that more aggressive action to reduce IHD risk factors, particularly among African American women, may be warranted. Researchers have discovered a strong link between a specific genetic abnormality in African Americans (blood platelet glycoprotein polymorphism) and premature IHD events, which may represent the first genetic platelet thrombogenic risk factor identified for IHD. Other research has shown there to be depressed epicardial and microcirculation blood flow unique to African Americans with hypertension. All of these findings, taken together, suggest that differences in mechanisms for IHD among African Americans and other population groups exist, and may provide the basis for improved recognition and treatment of IHD in African Americans.

The Institute is also funding other programs and centers specific to basic and clinical research on IHD in African Americans; for example, Collaborative Projects in Minority Health and Specialized Centers Of Research (SCORs) in IHD in Blacks. The recent addition of these two SCOR projects will greatly strengthen the body of research in this area.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in heart, lung, and blood diseases research?

Dr. Lenfant: This fiscal year the National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the NIH Office of Research on Minority Health, announced a new minority-specific initiative entitled "HBCU Research Scientist Award." The goals of the program are to: assist Historically Black Colleges and Universities (HBCU) strengthen and augment their human resources by recruiting an established research scientist, to enhance the career of the recruited research scientist, and strengthen other HBCU resources for biomedical and behavioral research in areas related to cardiovascular, lung, and blood health and disease, transfusion medicine, and sleep disorders.

It is our hope that HBCUs able to recruit an established scientist with ongoing research grants, will be able to attract additional research personnel. The new research grants and personnel will enhance the HBCU's ability to compete successfully for research and training grants from the NIH and other organizations. These programs will provide research and training opportunities for students and faculty on the HBCU campus and stimulate many of them to pursue careers in biomedical and behavioral sciences, thus increasing the number of minority scientists. The NHLBI also continues to support other previously implemented programs to increase the number of African American and other minority research investigators involved in heart, lung, and blood diseases research.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Dr. Lenfant, your Institute is to be commended for the outstanding job that it has done in outreach and public education. Your education programs have been remarkable in improving the public health. With respect to high blood pressure alone, the majority of the American people are keenly aware of how critical it is to have their blood pressure checked. Now, our challenge is to get them to take an active role in controlling it. If we could have the same degree of success with respect to blood pressure control, approximately how many lives could be saved each year in this area alone?

Dr. Lenfant: The latest data from our national surveys indicate that nearly 75 percent of all hypertensives are aware of their high blood pressure, yet only 25 percent are controlling it--that is reducing their blood pressure to less than 140/90 mm Hg. Nonetheless, controlling high blood pressure in 25 percent of hypertensives is saving lives.

This year approximately 500,000 Americans will die from coronary heart disease. Controlling high blood pressure could reduce deaths from coronary heart disease by about 25 percent. If 75 percent of hypertensive cases were controlled, then an additional 94,000 lives would be spared. This year, 150,000 Americans will die from stroke. Controlling high blood pressure could reduce stroke deaths by 50 percent. If 75 percent of hypertensives were controlled then one might assume that nearly 60,000 additional lives could be spared from stroke. Better control of high blood pressure would also reduce the number of deaths from kidney disease and peripheral and other vascular diseases. In addition, reducing high blood pressure would not only reduce deaths, but would also reduce the number of coronary, stroke, and renal events. The survivors of these events substantially increase the costs of our medical care system. Much of this could be prevented with better control of high blood pressure.

Mr. Stokes: There is so much more we can and must do. How much is included in the FY 97 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Lenfant: Based on what we knew about the budget in October 1995, we made the decision to allocate \$7.9 million for education programs in FY 1996 and \$7.1 million in FY 1997. This compares to \$10.6 million in FY 1995 and \$11.1 million in FY 1994.

Mr. Stokes: As these programs are funded in your research management and support account, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Lenfant: No, we have had to reduce these programs primarily because of the level of funding available under the Continuing Resolution for Research Management and Support.

Mr. Stokes: In which outreach areas are we hurting the most?

Dr. Lenfant: The reduction in RMS dollars has been felt across the board by each of the NHLBI national education programs and initiatives resulting in a significantly reduced capacity to be responsive to this mandate.

For example, a reduced printing budget has resulted in diminished dissemination efforts of treatment guidelines to core physician groups. Dissemination of two new treatment guidelines in asthma and obesity that are currently in development will be difficult to accomplish. Unfortunately, this comes at a time when an NHLBI-sponsored consumer services marketing study has clearly indicated that physician awareness of guidelines is dependent upon national direct mail campaigns. In another area, with close to 10,000 information requests received by NHLBI's Information Center each month, it will be difficult to continue to adequately meet this consumer demand. A major impact has also been felt in the area of public education campaigns on radio and television during the past year. Three entire media campaigns on cholesterol, blood pressure, and asthma have been deleted due to lack of funds thereby reducing exposure of millions of Americans to educational messages important to their health.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway with your Institute and the Office of Research on Minority Health?

Dr. Lenfant: The National Heart, Lung, and Blood Institute (NHLBI) has three major collaborative efforts with the NIH Office of Research on Minority Health (ORMH): a community outreach program involving black medical schools and Latino health organizations to make people aware of ways to reduce cardiovascular disease risk, a new program to help Historically Black Colleges and Universities recruit established research scientists to their campuses, and a program to

determine the most effective strategy for recruiting and retaining minority participants in the Dietary Approaches to Stop Hypertension Study (DASH).

Mr. Stokes: Are there specific projects in your Institute that are funded totally by the Office, and if so, which are they?

Dr. Lenfant: The NHLBI has two new projects funded entirely by the ORMH: a workshop on building collaborative partnerships between minority and nonminority institutions and an American Indian and Alaska Native outreach initiative.

Mr. Stokes: For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Lenfant: NHLBI projects supported entirely by the ORMH are listed below.

Title	Performance Period	ORMH Funds
Building Collaborative Partnerships Between Minority and Nonminority Institutions Workshop	FY 1996	\$65,500
American Indian and Alaska Native Initiative	FY 1996-1997	\$275,000

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the Office, if so what are they?

Dr. Lenfant: Projects co-funded by the NHLBI and ORMH include the Historically Black Colleges and Universities (HBCU) Research Scientist Award, a project on Recruitment and Retention of Minority Participants in Prevention-Oriented Clinical Trials, the minority supplements program, and the NHLBI National Cardiovascular Outreach Diffusion Network Initiative.

Mr. Stokes: Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the Office.

Dr. Lenfant: Based on what we know today, NHLBI projects co-funded by the ORMH are listed below.

Title	Performance Period	ORMH Funds	NHLBI Funds
HBCU Research Scientist Award	FY 1996-2002	\$7,750,000 (50%)	\$7,750,000 (50%)
Recruitment and Retention of Minority Participants in Prevention-Oriented Clinical Trials	FY 1996-1997	\$662,584 (16%)	\$3,412,385 (84%)
Support of New Minority Investigators	FY 1995	\$103,456 (3%)	\$3,016,705 (97%)
National Cardiovascular Outreach Diffusion Network Initiative	FY 1995	\$825,000 (62%)	\$500,000 (38%)

POTENTIAL HEALTH CARE COST SAVINGS

Mr. Hoyer: We have all spent a great deal of time in this Congress debating ways to reduce Medicare and Medicaid spending. Obviously, one way to do this is to improve medical treatments - and reduce the cost of those treatments -- for the elderly. Heart disease and strokes are two of the leading ailments for the Medicare and Medicaid population. Your testimony referred to several recent important research findings. Could you describe for us what other research in this area is being undertaken by the NHLBI, and elaborate on the potential savings in both the public and private sector as a result of this work?

Dr. Lenfant: The NHLBI currently supports a number of other programs related to heart disease and stroke that offer potential for substantial health care cost savings to the Nation. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a practice-based, randomized clinical trial of antihypertensive drug treatments, will determine whether any difference in mortality is associated with treatment using four classes of antihypertensive drugs. With approximately 50 million hypertensives in the U.S., finding the most effective treatment can save many lives. In addition, decreasing nonfatal cardiovascular events is expected to reduce costs associated with hypertension-associated morbidity. Since one of the drug classes being studied, the diuretics, has long been available in generic forms, a finding that they are as effective as the other classes of drugs could result in significant cost savings for antihypertensive therapy. Another NHLBI study with sizeable cost savings implications is the Beta-Blockers in Heart Failure Trial (BBHT). Although the main purpose of the BBHT is to determine whether beta-blocker therapy, when added to standard therapy for patients with moderate to severe heart failure, can reduce mortality, the study will also assess the effect of beta-blockers on heart function. Improved heart function can mean that heart failure patients may be able to avoid expensive episodes of hospitalizations.

Atrial fibrillation, a common form of cardiac arrhythmia, poses an increased risk for stroke. The NHLBI Clinical Trial of Management Strategies of Atrial Fibrillation in an Elderly Population will compare one drug-based therapy with a therapy comprising another class of drugs and/or catheter ablation. It is currently unclear which of the existing treatment options is preferable. Each offers potential benefits

but also poses some risks. Catheter ablation, for example, may avoid the need for some further drug intervention, but requires implantation of a pacemaker and treatment to prevent blood clots from forming. Thus, determination of the optimal treatment for atrial fibrillation, especially among the elderly, is likely to have substantial cost implications.

The Prevention of Events with Angiotensin Converting Enzyme Inhibitor Therapy (PEACE) trial will allow us to determine whether addition of an angiotensin converting enzyme (ACE) inhibitor to standard therapy for patients with known coronary heart disease and preserved left ventricular function can prevent cardiovascular mortality and reduce risk of heart attack. Since persons with known coronary heart disease are at high risk for heart attacks, finding additional therapeutic options can be expected to save lives and result in pronounced savings in emergency hospitalization costs. On the other hand, if the trial shows that ACE inhibitors offer no advantage, savings will immediately accrue in dispensing with an ineffective therapeutic intervention.

The NHLBI concurrently is attempting to reduce the economic costs of other serious diseases within its mandate. For example, chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death in the United States and a major cause of morbidity, is the subject of a current NHLBI multi-center clinical trial, Lung Health Study II. The objective of the study is to determine whether inhaled steroids slow the rate of decline in lung function and lower the incidence of respiratory morbidity in persons with COPD. If the findings show the treatment to be effective, notable long-term savings can be anticipated from a reduced need for oxygen support therapy and other clinical intervention. On the other hand, if the treatment is shown to be ineffective, then expenditures for ineffective treatments will be reduced.

ASTHMA

Mr. Hoyer: I am also interested in the advances made in the study of asthma, and the identification of genes which seem to control susceptibility to asthma. What applications of this research might we expect to improve the lives of asthma sufferers?

Dr. Lenfant: Recent advances in asthma research have disclosed the major role played by inflammation in the pathogenesis of asthma. Significant research efforts are currently underway to understand the cellular and molecular control of airway inflammation and the immune dysregulation that characterizes asthma.

Asthma also has an important genetic component in which several genes are likely to influence the expression of asthma and their effect is almost certainly modulated by environmental influences. Recent advances in molecular biologic techniques and analytic methods have now made it possible to identify the genes that cause many human diseases, including asthma. NHLBI-supported studies have already met with some success in identifying potential areas in the human genome that may be important in the regulation of the allergic state and in the development or progression of the inflammation associated with asthma. Currently, a genome-wide search is underway to identify all the genes that confer susceptibility to asthma. Understanding the complex genetic influence that may predispose 2 person to the development of asthma may be very important in elucidating the major defect(s) that cause asthma. Through identification of genes that influence asthma, the function(s) that these genes control may be determined and the defects identified. Understanding the genetics of asthma may open a completely new approach aimed at preventing the development of the disease itself rather than at preventing symptoms in patients who have already developed the illness. Such an approach would have an enormous health impact.

Mr. Hoyer: In your research on asthma and genetics, are you discovering that any genetic differences that appear to contribute to the large discrepancy between asthma death rates among the white and African American populations?

Dr. Lenfant: Although the reasons for the large discrepancy between death rates among the white and African American populations remain largely unresolved, it is possible that genetic factors play a significant role. In an important first step to understand how genetic factors influence the subsequent development of asthma, the NHLBI has undertaken Collaborative Studies on the Genetics of Asthma. The aim is to define the genes responsible for asthma. This study has enrolled the largest, most ethnically diverse, and thoroughly characterized sample of asthma families. An initial genome-wide screen of some of the individuals in the sample has just been completed and is being analyzed, including separate analyses by ethnic/racial group, to define genes that influence the development of asthma in those populations. Preliminary findings indicate promising areas where potential genes for asthma may be localized. At the present time, we do not know whether there are genetic variations that account for the differences in asthma mortality between whites and African Americans.

Mr. Hoyer: Is this discrepancy due to environmental or other factors?

Dr. Lenfant: NHLBI-supported studies have suggested that socio-economic factors contribute to this discrepancy. While differences in asthma mortality between whites and African Americans has not been fully assessed thus far, recent studies have shown that both the presence of genes predisposing to asthma and sensitivity to allergens early in childhood add significantly to the risk of developing asthma. Other related studies have shown that allergen (roach) exposure is an important contributor to asthma morbidity among inner-city children.

Mr. Hoyer: What can be done to correct this discrepancy?

Dr. Lenfant: Further research into the cellular and molecular basis of asthma should lead to the identification of the basic processes in asthma and lead to new and better treatment modalities to alleviate the suffering in all asthmatics.

Mr. Hoyer: How are the findings of your research in this area utilized by the CDC, the Public Health Service and others to try to reduce mortality rates among African Americans in this country?

Dr. Lenfant: The National Asthma Education and Prevention Program (NAEPP) uses the results of research to develop clinical practice guidelines for health professionals on diagnosis and management of asthma. A number of Federal government agencies are part of the NAEPP, including four representatives from the CDC in the areas of school health, environmental health, occupational health, and health statistics. The NAEPP also works with professional and voluntary health organizations to develop program activities and materials to reduce asthma morbidity and mortality in African American communities. The NAEPP has held several education training programs in cooperation with the National Medical Association to provide health professionals the latest information on effective asthma management. Moreover, the NHLBI has conducted five demonstration and education research projects in five locations, three of them in cities with large African American populations. The purpose of these investigations is to develop model asthma management programs that can be used by the CDC, other public health agencies, and the private sector that are interested in development asthma education programs in minority communities.

In addition, the NAEPP has funded three asthma community-education projects, two of which target African Americans. These projects encourage partnership among health professionals that participate on the NAEPP, community clinic personnel, and lay organizations such as the American Lung Association to develop and implement both professional education training and community-based education activities in these African American communities.

The NAEPP's strong focus on developing practice guidelines, patient education, and public education materials has been very useful in assisting State health departments, community clinics, hospital patient education programs, and community and lay organizations in carrying out a variety of educational programs to help people with asthma recognize warning signs and symptoms of asthma and to take appropriate action. These efforts will help to reduce both asthma morbidity and mortality.

An exciting opportunity for federal agencies involved in asthma to exchange information about advances in asthma research and treatment is provided through the NHLBI's Federal Liaison Group on Asthma. In this group, representatives from 10 federal agencies (including CDC) explore possibilities for collaboration in future research. Finally, NHLBI is co-sponsoring an upcoming meeting with other NIH Institutes, CDC, and EPA on Asthma and the Environment.

Mr. Hoyer: Dr. Lenfant, how does the National Asthma Education and Prevention Program contribute to increased asthma awareness among the general population?

Dr. Lenfant: The National Asthma Education and Prevention Program (NAEPP) consists of a collective partnership with 32 national, medical, professional, and community organizations as well as Federal government agencies coordinated by the NHLBI and committed to improving the prevention, management and control of asthma. It is a major vehicle to effect research translation and information dissemination to critical consumer audiences that suffer disproportionately from asthma. A major component of the NAEPP is its public education campaign to increase awareness of signs and symptoms of asthma by those with undiagnosed asthma. The campaign uses four key signs/symptoms: shortness of breath, wheezing, coughing, and tightness in the chest and uses radio, print media, airport posters and outdoor advertising. A secondary audience is patients with uncontrolled asthma. The major message of that campaign is to get those experiencing certain symptoms to see a doctor and find out if it is asthma.

Mr. Hoyer: Does this have an impact on minority populations?

Dr. Lenfant: Since minority populations, particularly African Americans and Hispanics experience disproportionate rates of asthma morbidity and mortality, the NAEPP has developed a national mass media campaign which has as its primary target audience those African Americans and Hispanics with asthma as well as health care providers. In addition, the NAEPP has captured the "lessons learned" from recent, NHLBI-funded demonstration and education research projects that targeted African American and Hispanic children to make this information available to the broader community. The NAEPP has also produced selected public education materials on asthma in Spanish to help facilitate the asthma awareness and education process in Hispanic communities.

JUSTIFICATION OF THE BUDGET ESTIMATES

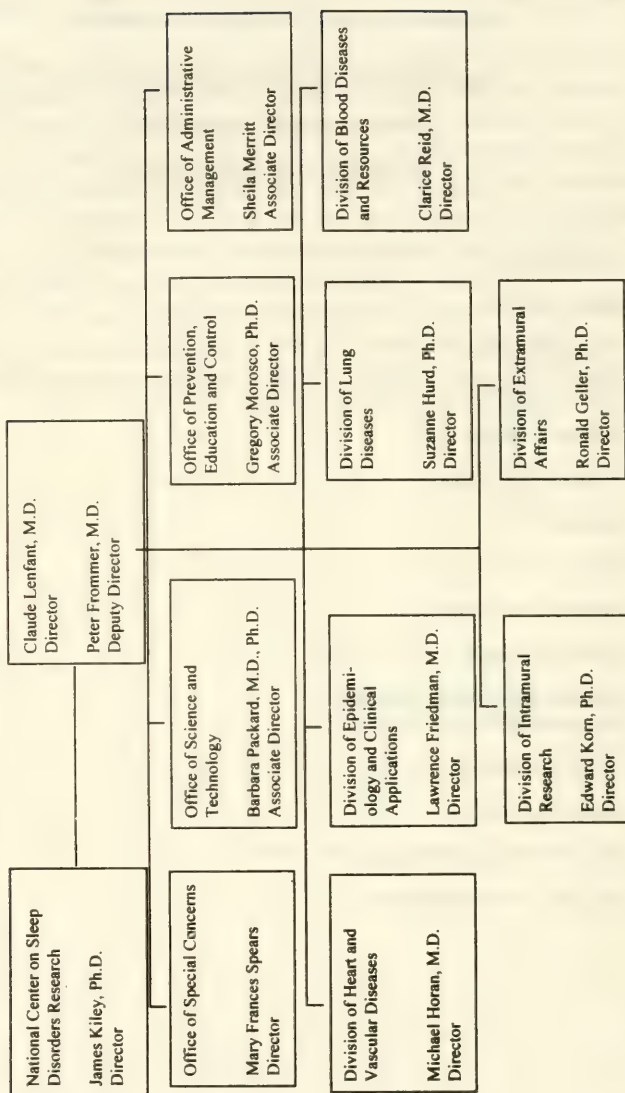
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

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NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Heart, Lung and Blood Institute

For carrying out section 301 and title IV of the Public Health Service Act

with respect to cardiovascular, lung, and blood diseases, and blood and blood

products, \$1,320,555,000.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92, and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National, Heart, Lung, and Blood Institute

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$1,259,590,000	\$1,355,866,000	\$1,320,555,000
Reduction in accordance with P.L. 103-333.....	-1,118,000		
Rescission in accordance with P.L. 104-19.....	-1,098,000		
Subtotal, adjusted appropriation.....	1,257,374,000	1,355,866,000	1,320,555,000
Real transfer from: Other NIH Institutes through the NIH Director's one percent transfer authority.....	2,125,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....		-57,925,000	
Comparative transfer to: HRSA for the National Marrow Donor Program.....	-15,360,000		
Comparative transfer to: Other NIH Institutes for Management Fund adjustment.....	-1,565,000		
Subtotal, adjusted budget authority.....	1,242,574,000	1,297,941,000	1,320,555,000
Unobligated balance, lapsing.....	-15,000	---	---
Total obligations.....	1,242,559,000	1,297,941,000	1,320,555,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1995--\$4,693,000; 1996--\$7,000,000; 1997--\$7,000,000.

Also excludes funding for HIV activities: FY 1995--\$55,485,000; FY 1997--\$58,115,000, included in the Office of AIDS Research, NIH.

Note: Excludes \$604,000 in FY 1995 and \$800,000 in FY 1996 for royalties.

Justification

National Heart, Lung, and Blood Institute

Authorizing legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1997 Authorization: Indefinite.

Budget Authority:

1995		1996		1997		Increase or	
Actual		Estimate		Estimate		Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
830	\$1,242,574,000	815	\$1,297,941,000	815	\$1,320,555,000	--	+\$22,614,000

General Statement

This document provides justification for the FY 1997 Non-AIDS activities of the National Heart, Lung, and Blood Institute. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national research program to prevent, diagnose, treat, and cure heart, blood vessel, lung and blood diseases, and sleep disorders; and to provide for an adequate and safe blood supply for the Nation. To achieve these goals, the Institute supports a comprehensive program of basic and clinical investigations, clinical trials, epidemiologic studies, and demonstration and education projects. This multifaceted approach has led to significant advances against several of the leading causes of death, and opened new and exciting avenues of research that could prevent these diseases and disorders. Such progress holds promise for improved quality of life for the American public and a reduction in the enormous impact these diseases have on the health care system.

The President's appropriation request of \$1,320,555,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NHLBI during the last five years has been as follows:

	<u>Amount</u>	<u>FTEs</u>
FY 1992	1,131,454,000	929
FY 1993	1,150,448,000	909
FY 1994	1,210,030,000	852
FY 1995	1,242,574,000	830
FY 1996	1,297,941,000	815

FY 1997 Budget Policy

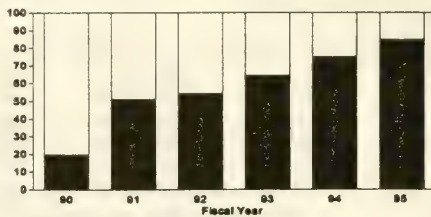
The President's Budget request for NHLBI is \$1,320,555,000, excluding AIDS, an increase of \$22,614,000, and 1.7 percent over the comparable 1996 level. Included in this increase is \$10,000,000 for the following NIH Special Emphasis Areas: (1) the biology of brain disorders; (2) new approaches to pathogenesis of disease; (3) new preventive strategies against disease; (4) the genetics of medicine; and (5) advanced instrumentation and computers in medicine and research. It is estimated that \$8,000,000 of these additional funds will support investigator initiated heart, lung, blood, or sleep research in these emphasis areas. The Institute plans to use \$2,000,000 of this increase to augment its sophisticated magnetic resonance imaging capability, which is part of its intramural research program.

In the FY 1997 President's Budget Request, the NHLBI support for research project grants (RPGs) would increase by 1.8% percent over FY 1996. This increase implements a change to the NIH Cost Management Plan to reflect the proposed overall increase of 1.64 percent over FY 1996 requested in the FY 1997 President's Budget. Thus, for FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on average, and the increase in the average cost of competing RPGs will be 2 percent or less than FY 1996. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 682 competing RPGs, an increase of 51 competing RPGs over FY 1996, and 2776 total RPGs, an increase of 88 total RPGs over FY 1996. Also included in the President's Request is a 2.2 percent increase in National Research Service Award stipend levels.

The budget will permit a variety of important ongoing programs to continue. For example, the Institute will increase support for the recently initiated "Historically Black Colleges and Universities Research Scientist Award." This program is a joint endeavor between the Institute and NIH's Office of Research on Minority Health, and uses funds provided in "other research" line on the mechanism table.

The Institute will continue its highly successful cost management program for research project grants. For each year since FY 1990, our strategy has enabled the Institute to fund a larger proportion of our new and competing renewal grants at Council recommended levels as shown in this graph entitled "NHLBI Research Project Grants".

NHLBI Research Project Grants*
Percent of Grants Funded at Council Recommended



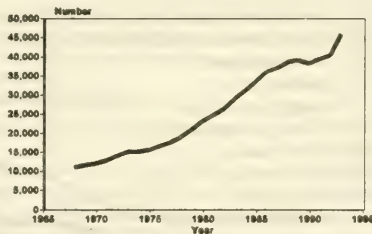
RESEARCH SUCCESSES AND CHALLENGES

Heart Failure

Heart disease is a long-term process that spans many decades of life and exemplifies the challenges faced by our research programs. Since the late 1960s, the decline in heart disease mortality has been substantial; it has occurred in men and women, in whites and blacks, and at all ages. Much of this declining mortality appears to be due to a decreasing case-fatality rate, that is, the proportion of patients who die shortly after a heart attack. While the decline in mortality is, of course, wonderful news, there are several substantial trade-offs. One consequence of our success in saving many heart disease patients from premature death is a sharp upturn in the prevalence of congestive heart failure.

Heart failure represents the final common pathway for most primary cardiovascular diseases, including coronary heart disease, hypertension, diseases of the heart muscle, and valvular and congenital malformations. Most treatments slow the course of the primary disease, but do not eliminate it. As a result, an increasing proportion of the population is living with heart disease and is susceptible to heart failure. Currently, heart failure affects an estimated 4.7 million Americans and causes about 45,000 deaths annually. Of particular concern is the observation that the death rate for heart failure for all ages has more than tripled since the late 1960s. Because heart failure is a major cause of hospitalization, its economic burden is substantial.

Annual Heart Failure Deaths



Fortunately, a comprehensive program of basic science studies is providing vital understanding that will result in better preventive or treatment strategies. A number of exciting clinical accomplishments have already resulted. For example, our own intramural researchers have uncovered the genetic defect that causes an inherited form of hypertrophic cardiomyopathy, a primary heart muscle disorder; as a consequence, it is possible to diagnose and treat this condition before onset of heart failure. Clinical trials and studies have identified effective treatments for heart failure, such as use of ACE (angiotensin-converting enzyme) inhibitors and heart transplantation. Patients with end-stage heart disease awaiting a suitable donor heart may be kept alive by use of a ventricular assist device that was developed through NHLBI-supported research and is now commercially available. The efficacy of an implantable automatic defibrillator (a device that corrects the abnormal rhythm that causes sudden death) is currently under investigation.

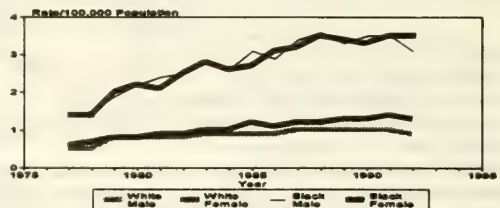
Recent developments in cellular and molecular techniques offer exciting promise for new strategies to restore heart function. Various forms of injury lead to the death of individual cardiac myocytes (heart muscle cells). Because adult cardiac myocytes cannot reproduce, their loss leads to heart failure. However, new studies raise the possibility that heart cell transplantation may be a feasible and effective approach to replacing these cells. First using mice, and then extending the work to dogs, researchers have shown that cardiac myocytes can be grafted from embryonic donors into adult hearts. The transplanted cells appear to become part of the recipient's heart tissue and to function normally. This cellular transplantation technique could be augmented through gene transfer technology to enhance cardiac myocyte function. Recent experiments using transgenic and gene targeting methods to create genetically altered mice suggest that a number of promising targets exist to improve the heart's pumping ability.

Finally, science has reached a new frontier in the area of heart transplantation. Although transplantation of human hearts is an effective treatment for end-stage heart failure, a major drawback is the shortage of donor organs. Recent developments using transgenic methods are now breaking down the barriers to using animal organs in human bodies. Specifically, transgenic pigs have been engineered to produce human proteins that suppress the body's immediate tendency to reject the "foreign" heart. When the hearts of such pigs were transplanted into baboons, they survived longer than had ever been possible. With further development, this "futuristic" approach to the problem of heart failure may become a reality.

Asthma

Asthma is a worldwide health problem that has been with us for centuries, and there is much evidence that its prevalence and severity are growing. In the United States, an estimated 12 million people have the disease, many of them children. It is becoming increasingly apparent that many commonly held notions about asthma—that children usually "outgrow" it, or that one can be "too old" to develop it—are erroneous, for asthma appears in all age groups. Deaths due to asthma are uncommon, but increasing, and those that occur tend to be sudden. Asthma creates burdens for individuals and the health-care system because it is chronic and leads to school absences, lost job productivity, and other activity limitations, as well as visits to physicians, emergency room utilization, and hospitalizations.

Asthma Death Rates



Recent years have witnessed tremendous advances in asthma treatment based on a new understanding that chronic and persistent inflammation of bronchial tissue is the driving force for this disease. Research has made it clear that continuous attention to this inflammatory process, rather than episodic response to acute attacks, is essential to break the vicious circle that leads to

airway obstruction. A variety of drugs are now available for this purpose, and the recent establishment of an Asthma Clinical Research Network will ensure rapid evaluation of new therapeutic strategies as they are developed.

The NHLBI has invested many years in the application of behavioral sciences research to the problem of asthma management. Model self-management approaches developed during the early 1980s have demonstrated that patient education and involvement is crucial to achieve optimal control. The National Asthma Education and Prevention Program has proven to be an effective vehicle for disseminating the results of this research. Its central theme, "Your Asthma Can Be Controlled: Expect Nothing Less," emphasizes that modern treatment should enable patients to control their symptoms, prevent attacks, be physically active, and breathe normally.

These improvements in asthma management have been very beneficial, but the ultimate goal of curing or preventing asthma is still challenging. No other chronic disease so vividly illustrates the interplay between genetic and environmental factors, and research in this area is the hope and promise of the future. New studies suggest that a person's genetic background interacts with a predisposing environment at critical stages of life to determine the pattern of response to these systems for the rest of life. Extension of such knowledge may ultimately pinpoint the timing and nature of preventive strategies.

A recent breakthrough is that scientists have now uncovered the location of major genes that control the allergy and hyperreactivity of the airways, two important risk factors for asthma. These findings represent the first important step in unraveling the genetic basis of asthma. It will then be possible to explore genetic interactions with environmental factors that play such an important role in causing the disease. Identification of the genes responsible for allergy and asthma is expected to lead to a better understanding of the primary defects in asthma, to development of better techniques for early diagnosis and disease prevention, and to new approaches for treatment.

Stem Cell Transplantation

NHLBI research and outreach programs have made bone marrow stem cell transplantation a common and successful procedure for treating leukemia and other blood and immune diseases. Through its intramural research program at the NIH Clinical Center and its recently established program, the Specialized Centers of Research in Stem Cell Biology, the Institute is advancing the state of stem cell transplantation science. New developments include techniques for overcoming incompatibility between donors and recipients, alternative sources of transplantable stem cells, and gene therapy and in utero transplantation to treat hereditary diseases.

Serologic tests for human leukocyte antigens (HLA), used by the immune system to distinguish the body's own cells from foreign cells, currently enable matching between donors and recipients. HLA incompatibility causes patients to suffer immune rejection of the bone marrow graft, as well as graft-versus-host disease (GVHD), in which immune cells from the donor marrow attack the patient's tissues as "foreign." Improved matching of marrow donors and recipients reduces the chance of immune rejection and GVHD, but even with the large numbers of marrow

donors now available, exact HLA matches in unrelated-donor transplantation are rare. In response to the growing need for unrelated-donor selection, the NHLBI spurred development of new DNA-based HLA typing techniques suitable for mass screening of any HLA type. DNA-based typing is now under development for class I HLA antigens to replace serologic methods and will become the standard within the next 1 to 2 years.

Another area of great progress is the use of stem cells collected after birth from discarded umbilical cord blood. Newborns have an undeveloped immune system, so these stem cells do not cause severe GVHD reactions in patients who receive them. An NHLBI-supported preliminary trial for transplanting these cells primarily in children has met with initial success, indicating that cord blood stem cells may be effective substitutes for bone marrow in some patients. Over 100 cord blood transplants have been performed to date and many of the critically ill children who received them are alive today thanks to this new technology. One important benefit of this technique is that exact HLA matches may not be as crucial for cord blood stem cell transplants as for bone marrow transplants.

Perhaps the most exciting long-range possibility for stem cell transplantation is gene therapy. NHLBI researchers are improving methods to purify stem cells and alter them genetically before transplanting them into patients with genetic disorders. The transplanted cells will supply a correct copy of the defective gene and may be the key to treating hereditary blood disorders such as sickle cell anemia, Cooley's anemia, and hemophilia. The NHLBI has also supported a groundbreaking demonstration of the potential benefits of in utero stem cell transplantation. Last year, two fetuses diagnosed at amniocentesis with rare fatal genetic disorders received bone marrow stem cells from their healthy fathers while still in the womb. Both children were born apparently healthy and have thrived with the functional genes supplied by their fathers' marrow.

These advances in stem cell technology are fast expanding the applicability of transplantation. The contributions arising from NHLBI-led research and targeted programs are improving patient survival without perfect donor matching. Faster than expected, they are leading to comprehensive treatments and, eventually, cures for leukemia, immune disorders, and genetic diseases that until now have been beyond the reach of medicine.

National Heart, Lung, and Blood Institute

Extramural Research Program

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1997 Authorization: Indefinite.

Budget Authority:

1995 Actual	1996 Estimate	1997 Estimate	Increase or Decrease
\$1,089,037,000	\$1,143,774,000	\$1,164,388,000	+ \$20,614,000

The major extramural programs, that is, those programs for which the Institute provides support but the research is actually conducted elsewhere, are the Heart and Vascular Diseases Program, the Lung Diseases Program, the Blood Diseases and Resources Program, and the Sleep Disorders Program. Extramural funding mechanisms utilized by the NHLBI include research projects grants, specialized centers of research and comprehensive research centers, several types of research career awards, cooperative clinical research, demonstration and education research, research training, and research contracts.

Funding for extramural programs during the last five years has been as follows:

	<u>Amount</u>
FY 1992	\$ 983,279,000
FY 1993	1,000,781,000
FY 1994	1,054,817,000
FY 1995	1,089,037,000
FY 1996	1,143,774,000

RESEARCH HIGHLIGHTSHeart and Vascular Diseases Program

Bypass Angioplasty Revascularization Investigation

Findings from the Bypass Angioplasty Revascularization Investigation (BARI) indicate that using angioplasty to relieve severe coronary artery blockages provides most patients with long-term health benefits comparable to those of bypass surgery, which is much more invasive and therefore more expensive. For nondiabetic patients and diabetics who did not require medication,

5-year mortality rates for both procedures were 9 percent; therefore, angioplasty appears to be an acceptable substitute for bypass surgery. However, for diabetics on medication, bypass surgery appears considerably more effective in the long run than angioplasty. Diabetics on medication had a 35 percent death rate for angioplasty, compared with 19 percent for bypass surgery. Based on these results, in September 1995 the NHLBI issued a clinical alert recommending bypass surgery over angioplasty for diabetic patients on medication. Findings from clinical trials such as BARI facilitate appropriate and cost-effective utilization of the latest life-saving technologies.

Hormone Replacement Therapy

Last year, initial results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial documented beneficial effects of hormone replacement therapy (HRT) on heart disease risk factors in postmenopausal women. New findings from PEPI show that HRT benefits older women and may be feasible even when started several years after the onset of menopause. The trial found that bone mass is actually gained—not just maintained—with HRT, and that more bone is gained in older women (55 to 64 years) than younger women (45 to 54 years). PEPI also demonstrated that HRT with estrogen plus progestin given continuously does not cause precancerous changes in the uterine lining (hyperplasia), a serious risk of estrogen-only therapy. Standard regimens that avoid hyperplasia call for intermittent use of progestin with continuous estrogen and are more complicated to follow. If the new combined HRT regimen does not cause other adverse effects, it will increase acceptability and ease of compliance with HRT and will have important public health implications for reducing heart disease and bone loss in older women. These findings will be particularly important for enabling long-term use of HRT and determining optimal timing and duration of treatment.

Drug Treatment for Hypertension

Calcium channel blockers have become the drugs most frequently used to treat high blood pressure, but new analyses have raised questions about their safety and risk of inducing heart attack compared with other antihypertensive drugs. In response to these concerns, the Institute convened a panel of experts and released a statement in September 1995 recommending caution for certain calcium channel blockers. The statement called for further safety evaluation while reinforcing existing research-based treatment guidelines for hypertension. The ongoing Antihypertensive and Lipid-Lowering Treatments to Prevent Heart Attack Trial (ALLHAT) will provide conclusive information on these drugs by comparing the ability of four classes of antihypertensive drugs, including calcium channel blockers, to reduce the rate of fatal and nonfatal heart attacks in patients with hypertension. Findings from ALLHAT will have strong implications for public safety and will provide new recommendations for prescribing antihypertensive drugs in ways that avoid serious side effects.

Child and Adolescent Trial for Cardiovascular Health

New results from the Child and Adolescent Trial for Cardiovascular Health (CATCH) indicate that school food service and physical education (PE) interventions are effective in reducing fat and saturated fat in school lunches and increasing the amount of moderate to

vigorous activity during PE classes. CATCH was a field trial to assess the outcomes of health interventions focusing on elementary schools, classroom curricula, and home programs for primary prevention of cardiovascular disease. Over 5,000 third-grade students from ethnically diverse backgrounds received interventions for 3 years. Students in the intervention group reported improved personal eating and physical activity behaviors and increased knowledge about nutrition. CATCH demonstrated that school policies and practices can be changed with minimal new resources and time. It provides an important model and interventions that other schools can use to improve the health of their students.

Clinical Trial Results with Cost Implications

Three NHLBI-supported clinical trials have just reported results that have significant implications for reducing the cost of medical care. A large study in heart failure patients established that digitalis treatment improves the symptoms of such patients, thereby reducing the need for hospitalization. A second trial, in patients who had undergone coronary artery bypass surgery using venous grafts, found that an aggressive approach to cholesterol lowering reduced the need for repeat revascularization procedures. The third trial provided convincing evidence that long-term prevention of hypertension is possible through a strategy of controlling weight and reducing sodium intake. These results provide important new direction for reducing the cost, as well as the suffering, associated with these widespread cardiovascular diseases.

Lung Diseases Program

Cystic Fibrosis

Researchers are learning how changes in the structure of CFTR, the chloride channel protein that is defective in cystic fibrosis (CF), prevent the protein from performing its normal functions. These discoveries have profound implications for new preventive and treatment strategies for CF. New studies reveal that, in addition to being a chloride channel itself, the CFTR protein also regulates other "alternate" chloride channels on the cell surface. These findings help explain how defects in CFTR can affect the chloride function of CFTR, its regulatory function on other non-CFTR chloride channels, or both. They suggest that new treatments for CF may have to correct both channel and regulatory function deficits to be most effective.

Chronic Obstructive Pulmonary Disease

One of the most important findings of the Lung Health Study (LHS) is that women benefit from smoking cessation even more than men. Few previous studies included enough women who quit smoking to allow evaluation of the gender effects of smoking cessation. The LHS, which included almost 2,200 women smokers, indicated that women who quit smoking had almost twice as much improvement in lung function as men who quit. Conversely, women who continued to smoke, or quit and then relapsed to smoking, lost lung function at a greater rate than men. Why women are more susceptible to the damaging effects of smoking is not yet known, but these results underscore the importance of smoking cessation for women. An extension is the LHS is

now testing the efficacy of steroid therapy in preventing loss of lung function in current and former smokers.

Lymphangioleiomyomatosis (LAM)

Increasing attention has recently been focused on LAM, a rare disease that affects almost exclusively young women of childbearing age. The disease is characterized by an abnormal type of muscle cell that grows throughout the lung and can obstruct the airways, blood vessels, and lymphatics. LAM is generally progressive, leading to increased pulmonary impairment and, eventually, death. Presently, there is no effective treatment for LAM except lung transplantation. The survival time following diagnosis has been reported to be less than 10 years, but recent reports show some patients living more than 20 years.

In March 1995, the NHLBI convened a small working group of scientists to review what is currently known about the disease and to identify future research directions. As a followup to that meeting, the NHLBI issued a program announcement to alert the scientific community of the Institute's interest in supporting research grants to study the molecular and cellular mechanisms of LAM. NHLBI staff have examined the logistics and feasibility of establishing a patient registry and lung tissue repository, and the Institute is optimistic that a grant application will be submitted to do so. The Institute has also prepared a Fact Sheet about LAM for patients and their families and friends.

Blood Diseases and Resources Program

Sickle Cell Disease

Recent results from the Prophylactic Penicillin Study indicate that children with sickle cell anemia who have not had a prior severe pneumococcal infection or surgical splenectomy can safely discontinue prophylactic penicillin after age 5, although they should still be monitored closely for fever. Children with sickle cell disease are at 100 times greater risk than normal infants and young children for life-threatening pneumococcal infections. Findings from a 1986 study showed that infants and young children with sickle cell disease who were given continuous oral penicillin treatment had 84 percent fewer cases of pneumococcal bacteremia than untreated children. As a result, treatment with penicillin from infancy is now standard care. However, because long-term antibiotic therapy poses the risk of promoting drug-resistant infections, a 7-year followup study investigated the risks, if any, of discontinuing prophylactic penicillin at 5 years of age, when these children are less vulnerable to pneumococcal infections. Application of the new findings is expected to reduce the risk of antibiotic-resistant infections in children with sickle cell anemia.

Gene therapy and bone marrow transplantation offer great hopes for curing sickle cell disease. Bone marrow transplantation has been successfully used by several investigators in Europe, as well as a small number in the United States. Although early reports are promising,

patient selection, donor availability, and complications of the procedure continue to be potential problems that prevent widespread use of this therapeutic modality today.

Basic research on gene therapy is advancing, with the possibility of inserting normal genes for hemoglobin production into bone marrow precursor or stem cells, thus enabling the production of normal hemoglobin. The ability to obtain highly enriched quantities of stem cells from cord blood, peripheral blood, and bone marrow will facilitate continued advances in gene transfer strategies. However, the efficiency of gene transfer must be improved before this procedure has the potential for therapeutic benefit in sickle cell disease. This approach is receiving active attention by many researchers around the country, who are optimistic that a cure for sickle cell disease can be achieved within the next decade.

Transfusion Biology and Medicine Specialized Centers of Research

Three new Specialized Centers of Research (SCORs) in Transfusion Biology and Medicine have been established to focus on several areas of blood transfusion that are essential for optimal use and improvement of transfusion therapy. The SCORs will explore immunological aspects of transfusion, development of innovative therapies, structure-function relationships of blood cell surface components, and optimal timing of red blood cell transfusion. These new research efforts will increase the effectiveness of blood transfusion, enhance understanding of its physiological effects on the recipient, and expand the range of transfusion-based therapies to meet special needs.

Safety of the Blood Supply

The NHLBI monitors emerging diseases that may threaten blood transfusion safety. A recent example is Creutzfeldt-Jakob disease (CJD), a rare but fatal degenerative brain disease. No cases of transfusion-borne transmission have been reported to date; however, because the agent for disease transmission is still unknown and the disease has a very long incubation period, the NHLBI supports research on CJD and blood transfusion and on new tests to hasten detection of the CJD agent. These efforts will provide the tools to avert any potential CJD threat to the Nation's blood supply.

Sleep Disorders Research

Sleep Apnea in Women

Recent studies suggest that the reported lower rates of sleep apnea in women compared with men may be due, in part, to physiological differences that influence the quality of breathing during sleep. Research comparing electrical activity of the tongue muscle and upper airway resistance in healthy men and women while awake found immediate and sustained tongue muscle activity response to simulated nerve signaling in normal women but no significant response in normal men. The cause of the increased response in women during wakefulness and the extent to which it may persist during sleep are not yet known. If the greater responsiveness of tongue and other airway muscles in women is also present during sleep, it may protect against sleep apnea by

rendering the airway more stable and less collapsible. These findings illustrate the potential of new approaches to understanding the etiology of sleep apnea and developing effective treatment strategies for it.

Sleep Apnea and Automobile Accidents

Preliminary findings from ongoing NHLBI-supported studies indicate that sleep apnea, or interrupted breathing during sleep, increases a driver's risk of automobile accidents. Persons with mild sleep apnea had four times greater risk of having one or more motor vehicle accidents than subjects without the disorder, and subjects with severe sleep apnea were eight times more likely to have multiple accidents. Driving risks increased with sleep apnea even after accounting for differences in gender, miles driven, and alcohol use. These results suggest that a significant fraction of motor vehicle accidents may be preventable through recognition and treatment of sleep apnea, and underscore the need to educate physicians and sleep apnea patients on risks associated with this disorder.

National Sleep Disorders Research Plan

The authorizing legislation for the National Center on Sleep Disorders Research (NCSDR) required that the Sleep Disorders Research Advisory Board prepare a sleep disorders research plan for the Director, NIH. That task is now complete, and the plan recommends a combination of basic research on the molecular mechanisms of sleep, patient-oriented clinical studies, and applied research on sleep, sleepiness and treatment of sleep disorders. Basic research recommendations focus on the genetic and molecular mechanisms of sleep, one of the most promising frontiers for sleep research. Evidence is mounting that circadian rhythms, which determine the timing of sleep-wake cycles and other daily fluctuations, are under genetic control. Several recently discovered genes have been shown to regulate the circadian clock in mice, fruit flies, and other organisms, and mutation of these genes is associated with circadian rhythm disorders. These findings are beginning to pave the way towards understanding the relationship between the biological clock and the sleep/wake cycle. Although genetic techniques have led to significant insights into circadian rhythm biology, these molecular approaches have not been used to develop an understanding of the fundamental mechanisms of sleep control. Thus, the Institute will seek to increase research efforts in this area. A better understanding of the fundamental neurobiologic mechanisms that underly sleep disorders may lead to innovative therapies and have a strong impact on traffic accidents, worker absenteeism, and other public burdens caused by sleep disorders.

National Heart, Lung, and Blood Institute

Intramural Research Program

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1997 Authorization: Indefinite.

Budget Authority:

1995		1996		1997		Increase or Decrease	
<u>Actual</u>		<u>Estimate</u>		<u>Estimate</u>			
FTE	BA	FTE	BA	FTE	BA	FTE	BA
376	\$95,638,000	373	\$100,737,000	373	\$102,737,000	--	+ \$2,000,000

The Intramural Research Program of the Institute conducts an exciting and diverse basic and clinical research program on diseases of the heart, blood vessels, lung, and blood in facilities at the National Institutes of Health. The Institute continues cutting edge research that has resulted in significant advances in gene therapy and bone marrow transplantation, and treatment of hemoglobin disorders. Orientation of the research program is moving toward macromolecular structure, cellular biology, molecular biology, genetics, and molecular medicine, including gene therapy. Noteworthy advances and our future plans are described in the material that follows.

Funding for this program during the last five years has been as follows:

	<u>Amount</u>	<u>FTEs</u>
FY 1992	\$91,295,000	445
FY 1993	92,948,000	433
FY 1994	98,583,000	396
FY 1995	95,638,000	376
FY 1996	100,737,000	373

RESEARCH HIGHLIGHTSHypertrophic Cardiomyopathy and Sudden Cardiac Death

Researchers have developed an innovative approach to treating hypertrophic cardiomyopathy (HCM), or thickening of the heart muscle. Using a specially designed pacemaker, it is possible to relieve the obstruction of blood flow by altering the heartbeat. HCM is an often unrecognized genetic disease. It is the leading cause of sudden death in otherwise healthy young people such as athletes, and it affects blacks disproportionately. HCM patients with severe symptoms who fail to benefit from drug therapy are often advised to undergo a heart operation to shave down the thickened muscle mass. The pacemaker may render this kind of major heart surgery unnecessary, particularly in young patients.

Research on the molecular and genetic basis of HCM is leading to important diagnostic and treatment prospects. Over 2,000 families with HCM are being followed at the NIH Clinical Center. Several different genetic abnormalities have been identified in the study families and can be detected in a large number of children who do not yet have discernible heart thickening. Determining the HCM severity and outcome resulting from each type of gene defect will provide a way to predict high or low risk of sudden cardiac death based on the type of abnormality a patient has. The research may also lead to development of gene-based therapies to correct the abnormality or its effects and prevent heart muscle thickening in children with HCM.

Angiogenesis--Progress in Safety Studies

Drug therapy to promote angiogenesis (growth of new blood vessels) is emerging as a new weapon in the battle against heart disease. Most heart disease is caused by atherosclerosis, which is currently treatable only by surgery to unclog or bypass the clogged arteries. Angiogenic drugs offer the possibility of fostering the growth of new blood vessels that may be able to form natural "bypasses" around blocked segments of arteries. One such agent, basic fibroblast growth factor, has been found safe and highly effective in laboratory studies and is now being evaluated for safety in humans. By enabling the body to grow natural bypasses, angiogenic therapy could reduce the need for extensive heart surgeries and have a major impact on the treatment of heart disease.

Advances in Noninvasive Imaging of the Heart

Magnetic resonance imaging (MRI) is now being used for noninvasive, detailed investigation of the cardiovascular system. New methods developed by NHLBI intramural researchers use an advanced 4.0-Tesla magnet system as well as conventional MRI scanners to determine blood vessel elasticity or compliance as a measure of vascular disease. Cardiac blood volume, blood flow, and oxygen delivery to the tissues can also be measured under normal and experimental conditions. MRI can also map local movements of the heart to determine the location and severity of ischemia (insufficient blood flow to the heart muscle) or other forms of cardiac disease. These new noninvasive techniques hold great promise for increasing the precision of diagnosis for cardiovascular problems prior to surgery and could become standard clinical tools in the near future.

Chest Pain and the Sensitive Heart

New findings indicate that many patients who experience chest pain without any apparent coronary abnormalities (known as "Syndrome X"), may actually have abnormal cardiac pain perception, or "sensitive heart syndrome." Drugs for managing chronic pain syndromes are effective in treating symptoms in these patients. A drug that increases the heart rate and contractile intensity is being used in a new diagnostic test to investigate whether symptoms of Syndrome X are caused by this abnormal sensory perception in the heart or another condition, microvascular angina (abnormal function of the small blood vessels). In cases where abnormal neural sensitivity to pain is diagnosed as the cause, patients, most of whom are women, should be

able to obtain relief with painkillers and avoid being admitted to coronary care units or undergoing cardiac catheterizations for this condition.

LAM and Implications for Understanding of Smooth Muscle

Lymphangioleiomyomatosis (LAM), a severe, always fatal lung disease affecting primarily women of childbearing age, has become a valuable model system for studying proliferation of abnormal smooth muscle cells in more common diseases. Though the disease itself is rare, the abnormal smooth muscle cell development of LAM has similarities to melanoma, a highly malignant cancer, and tuberous sclerosis complex, a genetic disease characterized by the widespread growth of tumors. LAM studies thus far have led to the demonstration of genes that are expressed in cancer cells and in lung biopsies from LAM patients, but not in normal lung tissue. Current efforts to identify the function of these genes in smooth muscle and cancer cell growth may also lead to significant discoveries about the molecular and genetic mechanisms of smooth muscle proliferation found in atherosclerosis.

National Heart, Lung, and Blood Institute

Research Management and Support

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1997 Authorization: Indefinite.

Budget Authority:

1995 Actual		1996 Estimate		1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
454	\$57,899,000	442	\$53,430,000	442	\$53,430,000	--	---

The Research Management and Support budget activity provides funds for the overall management of the Institute's programs; for the education programs in the Office of Prevention, Education, and Control; and for international cooperative research activities. One of the most important uses for these funds relates to the coordination of activities that cut across program lines such as the National Center on Sleep Disorders Research, minority health and training, women's health issues, AIDS research, international cooperative research agreements, and administrative initiatives, for example, new agreements with the private sector authorized by the Federal Technology Transfer Act.

Funding for this program during the last five years has been as follows:

	<u>Amount</u>	<u>FTEs</u>
FY 1992	\$56,880,000	484
FY 1993	56,719,000	476
FY 1994	56,630,000	456
FY 1995	57,899,000	454
FY 1996	53,430,000	442

In FY 1997, the Institute will continue to evaluate the way in which we plan and carryout our programmatic and business functions, while we provide proper stewardship over the resources entrusted to us. This task has become even more important with continuing implementation of changes resulting from the National Performance Review and the FY 1996 reductions in FTEs and dollar resources available for these purposes.

The Institute views the changes that are occurring as positive. We have implemented numerous streamlining activities to simplify and expedite the review of grants and contracts. We have reorganized and increase utilization of teams for those tasks that can benefit from such an

approach. We have delegated more authority to our managers and supervisors as they are delegated by NIH to us. We have increased our investment in information technology to reduce duplication of effort, and expedite the analysis and transmission of data. We are implementing a new performance appraisal system that will reduce paperwork, while still providing appropriate feedback and recognition for our staff. We have simplified administrative procedures in property management, local travel, and messenger service. We continue to develop ideas for further change.

One of the most significant NIH activities is the development of the concept of competitive service centers. As an alternative to each organizational component developing its own capability to carry out certain functions, the Institute used its staff and expertise to develop service centers in the areas of procurement, committee management, and technology transfer, which are providing these services to those NIH components willing to participate. Although this concept is new and only recently implemented, the approach shows promise and will be thoroughly evaluated as we proceed.

Education Programs

The Institute conducts its highly effective public and professional education programs and information dissemination activities primarily with funds provided to the Research Management and Support budget activity. Because resources to carry out these programs are increasingly constrained, the Institute is evaluating its efforts, and seeking a variety of new approaches to carry out its mandate such as greater use of the World Wide Web. However, it is important to continue these programs since they are often the vehicle for translating results from our investments in research to improvements in public health.

National Heart, Lung, and Blood Institute

Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Research grants:						
Research projects						
Noncompeting	1,815	\$565,297,000	1,966	\$625,448,000	1,983	\$616,635,000
Admin. supplements	(91)	4,094,000	(80)	3,126,000	(80)	3,189,000
Competing:						
Renewal	298	93,158,000	260	84,900,000	282	92,941,000
New	401	101,420,000	369	96,766,000	398	105,103,000
Supplemental	2	1,871,000	2	1,690,000	2	1,853,000
Subtotal, competing	701	196,449,000	631	183,356,000	682	199,897,000
Subtotal, res. projects	2,516	765,840,000	2,597	811,930,000	2,665	819,721,000
SBR/STTR	158	23,749,000	133	23,998,000	111	30,981,000
Total, res. projects	2,674	789,589,000	2,730	835,928,000	2,776	850,702,000
Research Centers						
Spec./comp. centers	75	106,124,000	75	106,732,000	75	106,732,000
Other research						
Res. career program	354	30,341,000	378	32,884,000	366	32,533,000
Coop. clin. research	43	16,763,000	38	16,514,000	42	18,514,000
Minority biom. research		2,313,000		2,803,000		2,803,000
Other res. related	20	5,224,000	35	4,687,000	34	4,687,000
Subtotal, other research	417	54,641,000	451	56,888,000	442	58,537,000
Total, research grants	3,166	950,354,000	3,256	999,548,000	3,293	1,015,971,000

Training					
Individual awards:					
Noncompeting					
Competing	125	3,706,000	122	3,642,000	116
Subtotal, individual	116	3,397,000	101	3,728,000	107
	241	7,103,000	223	7,370,000	223
Institutional awards:					
Noncompeting	1,135	31,257,000	1,152	35,894,000	1,300
Competing	314	9,676,000	183	5,849,000	35
Subtotal, institutional	1,449	40,933,000	1,335	41,743,000	1,335
Total, training	1,690	48,036,000	1,558	49,113,000	1,558
Research & development contracts					
	165	90,647,000	166	95,113,000	159
	FTEs		FTEs		FTEs
Intramural research	376	95,638,000	373	100,737,000	373
Research management and support	454	57,899,000	442	53,430,000	442
Extramural construction		0		0	0
Total (Clinical Trials)	830	1,242,574,000	815	1,297,941,000	815
		(90,414,000)		(92,694,000)	
					1,320,555,000
					(96,606,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Activity

(Dollars in thousands)

	1993 Actual		1994 Actual		1995 Actual		1996 Estimate		1997 Estimate		Change	
	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
Extramural Research:												
Heart and vascular diseases program.....	--	\$624,010	--	\$642,414	--	\$664,516	--	\$698,641	--	\$714,041	--	\$15,400
Lung diseases program.....	--	199,309	--	212,647	--	215,326	--	219,860	--	223,358	--	3,498
Blood diseases and resources program.....	--	168,517	--	186,917	--	196,049	--	211,512	--	212,978	--	1,466
Center for sleep disorders research.....	--	8,898	--	12,840	--	13,146	--	13,761	--	14,011	--	250
Subtotal, extramural.....		1,000,734		1,054,818		1,089,037		1,143,774		1,164,388		20,614
Intramural research.....	433	92,948	396	98,564	376	95,638	373	100,737	373	102,737	--	2,000
Research management and support.....	476	56,719	456	56,620	454	57,884	442	53,430	442	53,430	--	---
Total, obligations.....	909	1,150,401	852	1,210,002	830	1,242,559	815	1,297,941	815	1,320,555	--	22,614
Unobligated balance, lapsing.....	--	47	--	28	--	15	--	---	--	---	--	---
Total, budget authority.....	909	1,150,448	852	1,210,030	830	1,242,574	815	1,297,941	815	1,320,555	--	22,614

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National Heart, Lung, and Blood Institute

Summary of Changes

1996 Estimated budget authority.....	\$1,297,941,000
1997 Estimated budget authority.....	1,320,555,000
Net change.....	22,614,000

	1996 Current Estimate Base		Change from base	
	FTEs	Amount	FTEs	Amount
Changes:				
A. Built-in:				
1. Intramural Research				
a. Within grade increase.....		\$27,719,000		\$391,000
b. Annualization of				
January 1996 pay raise.....		27,719,000		174,000
c. January 1997 pay increase.....		27,719,000		626,000
d. Service and Supply				
fund increase.....		15,863,000		349,000
e. Payment for centrally				
furnished services.....		36,261,000		-220,000
f. Increased cost of				
laboratory materials				
and other supplies.....		20,894,000		459,000
Subtotal.....				1,779,000
2. Research Management				
and Support				
a. Within grade increase.....		29,816,000		517,000
b. Annualization of				
January 1996 pay raise.....		29,816,000		187,000
c. January 1997 pay increase.....		29,816,000		671,000
d. Unemployment compensation				
and FECF.....		276,000		11,000
e. Service and Supply				
fund increase.....		5,318,000		117,000
f. Payment for centrally				
furnished services.....		12,072,000		-826,000
g. Increased cost of				
laboratory materials				
and other supplies.....		6,224,000		137,000
Subtotal.....				814,000
Total, Built-in.....				2,593,000

Summary of Changes--continued

	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting.....	1,966	628,574,000	17	-8,750,000
b. Competing.....	631	183,356,000	51	16,541,000
c. SBIR/STTR.....	133	23,998,000	-22	6,983,000
Total.....	2,730	835,928,000	46	14,774,000
2. Research career program.....	378	32,884,000	0	-351,000
3. Coop. Clinical research.....	38	16,514,000	4	2,000,000
4. Other research related.....	35	4,687,000	-1	0
5. Individual training awards.....	223	7,370,000	0	162,000
6. Institutional training awards.....	1,335	41,743,000	0	918,000
7. Research and development contracts.....	166	95,113,000	-7	3,111,000
	FTEs	Amount	FTEs	Amount
8. Intramural research				
a. Program decrease.....	373	100,737,000	0	-1,779,000
b. Special Emphasis	0	0	0	2,000,000
Total.....	373	100,737,000	0	221,000
9. Research management and support.....	442	53,430,000	0	-814,000
Subtotal.....				20,021,000
Total changes.....				22,614,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

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National Heart, Lung, and Blood Institute

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	815	815	---
Full-time equivalent of overtime and holiday hours.....	4	4	---
Average SES salary.....	\$109,539	\$112,825	3,286
Average GM/GS grade.....	10.30	10.00	-0.30
Average GM/GS salary.....	\$46,832	\$48,237	1,405
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).....	\$78,136	\$80,480	2,344
Average salary of ungraded positions.....	\$36,122	\$37,205	1,083
Personnel compensation:			
Full-time permanent.....	\$34,287,000	\$35,464,000	\$1,177,000
Other than full-time permanent.....	6,338,000	6,571,000	233,000
Other personnel compensation.....	1,844,000	1,905,000	61,000
Special personnel service payments.....	4,651,000	4,829,000	178,000
Total personnel compensation.....	47,120,000	48,769,000	1,649,000
Personnel benefits.....	10,144,000	10,492,000	348,000
Benefits for former personnel.....	271,000	281,000	10,000
Subtotal pay costs.....	57,535,000	59,542,000	2,007,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Travel.....	909,000	900,000	-9,000
Transportation of things.....	234,000	231,000	-3,000
Rental payments to GSA.....	1,000	1,000	—
Rental payments to others.....	583,000	576,000	-7,000
Communications, utilities, and miscellaneous charges.....	3,061,000	3,023,000	-38,000
Printing and reproduction.....	627,000	627,000	—
Other contractual services:			
Advisory and assistance services.....	1,321,000	1,311,000	-10,000
Other services.....	2,633,000	2,603,000	-30,000
Purchases from govt. accounts.....	86,143,000	86,255,000	112,000
Operation and maintenance of facilities.....	1,351,000	1,331,000	—
R&D Contracts.....	73,513,000	76,876,000	3,363,000
Medical care.....	2,954,000	2,919,000	-35,000
Operation and maintenance of equipment.....	1,882,000	1,856,000	-26,000
Subtotal, other contractual services.....	169,797,000	173,151,000	3,354,000
Supplies and materials.....	9,590,000	9,487,000	-103,000
Equipment.....	6,781,000	6,691,000	-90,000
Lands and structures.....	2,000	2,000	—
Grants, subsidies, & contributions.....	1,048,661,000	1,066,164,000	17,503,000
Insurance claims and indemnities.....	155,000	155,000	—
Interest and dividends.....	5,000	5,000	—
Total budget authority by object.....	1,297,941,000	1,320,555,000	22,614,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

	<u>Administrative Costs</u>		Increase or Decrease
	1996 Estimate	1997 Estimate	
Personnel Compensation:			
Full-Time Permanent (11.1).....	\$34,287,000	\$35,464,000	\$1,177,000
Other than Full-Time Permanent (11.3).....	6,338,000	6,571,000	233,000
Other Personnel Compensation (11.5).....	1,844,000	1,905,000	61,000
Special Personal Service Payments (11.8).....	4,651,000	4,829,000	178,000
Total Personnel Compensation (11.9).....	47,120,000	48,769,000	1,649,000
Civilian Personnel Benefits (12.1).....	10,144,000	10,492,000	348,000
Benefits for Former Personnel (13.0).....	271,000	281,000	10,000
Travel (21.0).....	909,000	900,000	-9,000
Transportation of Things (22.0).....	234,000	231,000	-3,000
Rental Payments to Others (23.2).....	583,000	576,000	-7,000
Communications, Utilities, and Miscellaneous Charges (23.3).....	3,061,000	3,023,000	-38,000
Printing and Reproduction (24.0).....	627,000	627,000	0

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Consulting Services (25.1).....	621,000	621,000	0
Other Services (25.2).....	2,633,000	2,603,000	-30,000
Purchases from Government Accounts (25.3).....	55,113,000	56,143,000	1,030,000
Operation and Maintenance of Facilities (25.4).....	1,351,000	1,331,000	-20,000
Medical Care (25.6).....	2,954,000	2,919,000	-35,000
Operation and Maintenance of Equipment (25.7).....	1,882,000	1,856,000	-26,000
Supplies and Materials (26.0).....	<u>9,590,000</u>	<u>9,487,000</u>	<u>-103,000</u>
Total.....	137,093,000	139,859,000	2,766,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Significant Items in House and Senate
Appropriations Committee Reports1996 House Appropriations Committee Report languageItem

Heart disease in African Americans - The house in its report 104-209, page 62 states that "Although death rates for heart disease have dropped significantly over the past 20 years, the drop has been much greater for whites than for African Americans. The Committee urges the Institute to expedite research to advance understanding of heart disease in African Americans, using molecular biology, cellular and organ physiology and clinical medicine."

Action Taken or to be Taken - The Institute has funded new Specialized Centers of Research on Ischemic Heart Disease in Blacks to help address these important issues.

Item

Asthma - The house in its report 104-209, page 62 states that, "It is now recognized that asthma is a complex, chronic disease, triggered by a number of factors and requiring multiple medications for treatment and control. The Committee is particularly concerned about higher incidence and death rate among children living in poverty, including the disproportionately high incidence in African Americans and other minorities. The Committee urges the Institute to enhance its focus on asthma in at-risk populations. The Institute should also strengthen its collaboration in this area with both NICHD and NIAID. In addition, the Committee encourages NHLBI to consider supporting the development and evaluation of innovative model school programs to increase identification and appropriate referral of children with uncontrolled asthma and reduce exposure to known allergens and irritants."

Action Taken or to be Taken - The Institute continues to collaborate with NIAID on genetics of asthma and with NICHD on asthma in pregnancy, and will continue to seek opportunities for further productive collaboration. In FY 1996 the Institute has funded an initiative on interventions to improve asthma management and prevention at school, which seeks to assure optimal asthma control and the continued involvement of children with asthma in school activities.

Item

Hemophilia - The house in its report 104-209, page 63 states that "the Committee remains deeply concerned about insuring the safety of the nations blood supply and is concerned over the recent withdrawal of blood products contaminated with Creutzfeldt-Jakob Disease (CJD). Therefore,

potential impact of CJD on the safety of the U.S. blood supply and specifically on people with bleeding disorders and transfusion recipients."

Action Taken or to be Taken - No cases of transfusion-borne transmission of the CJD virus have been reported to date; however, because the agent for disease transmission is still unknown and the disease has a very long incubation period, the NHLBI supports research on CJD and blood transfusion and on new tests to hasten detection of the CJD agent. CDC and FDA are cooperating with us in these efforts.

Item

Nutrition - The house in its report 104-209, page 63 states that, "The Committee urges the NHLBI to continue its nutrition research initiative. The Committee also encourages NHLBI to include nutrition research in its critical care medicine initiative. NHLBI has been supporting productive research to prevent heart disease involving reduced dietary fat among children and lowering of triglyceride levels through diet."

Action Taken or to be Taken - An NHLBI task force on research in critical care medicine recognized the importance of nutritional support in patient care. As a result, the Institute will seek to support additional research, for example, studies that will help determine adequate intake of specific essential nutrients while avoiding excessive intake of calories, glucose, and fat.

Item

Sleep disorders - The house in its report 104-209, page 63 states that "The Committee notes the continued development of the National Center for Sleep Disorders Research and the expansion of the Center's research portfolio. The Committee is concerned, however, that the national sleep disorders education campaign has not moved forward, despite the Committee's encouragement. The Committee also recommends continued development of a plan for scientific collaboration among the National Center and other NIH institutes."

Action Taken or to be Taken - The sleep disorders education program has begun. The Institute has published two pamphlets on sleep apnea, and launched radio, television, and print public announcements. NHLBI has also produced and distributed educational materials related to more general sleep problems such as sleep deprivation, and falling asleep while driving a vehicle.

1996 Senate Report LanguageItem

Heart disease in women and minorities - The Senate in its report 104-209, page 71 states that "African Americans have disproportionately higher death rates from heart disease than whites. Although death rates for heart disease have dropped significantly over the past 20 years, the drop has been much greater for whites than for African-Americans. The committee urges the Institute to expand research to advance understanding of heart disease in African-Americans, using molecular biology, cellular, and organ physiology, and clinical medicine."

Action Taken or to be Taken - The Institute has funded new Specialized Centers of Research on Ischemic Heart Disease in Blacks to help address these important issues.

Item

National Center on Sleep Disorders Research - The Senate in its report 104-209, page 73 states that "The Committee notes the continued development of the National Center for Sleep Disorders Research and the expansion of the Center's research portfolio and commends the Institute for its work in fiscal year 1995. The Committee strongly supports the development and implementation of a vigorous national sleep disorders public education campaign. The Committee requests that the Institute work in cooperation with the National Highway Traffic safety Administration on the development and implementation of such a public awareness campaign."

Action Taken or to be Taken - The sleep disorders education program has begun. The Institute has published two pamphlets on sleep apnea, and launched radio, television, and print public announcements. NHLBI has also produced and distributed educational materials related to more general sleep problems such as sleep deprivation, and falling asleep while driving a vehicle.

Item

Hemophilia - The Senate in its report 104-209, page 73 states that "The Committee supports expansion of NHLBI's very promising hemophilia gene therapy program . . . Creutzfeldt-Jakob Disease (CJD). Therefore, the Committee requests NHLBI to work in collaboration with CDC and FDA to investigate the potential impact of CJD on the safety of the U.S. blood supply and specifically on people with bleeding disorders and transfusion recipients. The Committee requests that the Director be prepared to report to the Committee during the fiscal year 1997 budget hearings on steps taken to address this issue."

Action Taken or to be Taken - No cases of transfusion-borne transmission of the CJD virus have been reported to date; however, because the agent for disease transmission is still unknown and the disease has a very long incubation period, the NHLBI supports research on CJD and blood transfusion and on new tests to hasten detection of the CJD agent. CDC and FDA are cooperating with us in these efforts.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Authorizing Legislation

PHS ACT/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Appropriation	1997 Amount Authorized	1997 Budget Request
Research and Investigation.....	Section 301 42§241	Indefinite		Indefinite	
National Heart, Lung, and Blood Institute.....	Title IV, Parts B and C 42§284c	Such sums as necessary	\$1,248,828,000	Such sums as necessary	\$1,270,362,000
National Research Service Awards.....	Section 487(d) 42§288	Such sums as necessary	49,113,000	Authorization is pending	50,193,000
Total Adjusted Budget Authority.....			1,297,941,000		1,320,555,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Appropriations History

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation 1/
1988	\$821,887,000	\$990,808,000 2/	\$990,646,000	\$965,536,000
1989	1,015,471,000 3/	1,018,903,000	1,056,603,000	1,045,985,000
1990	1,039,846,000 4/	1,090,930,000	1,091,597,000	1,087,524,000 5/
1990 Sequester				-15,170,000
1991	1,112,502,000	1,135,589,000 6/	1,137,235,000	1,126,942,000 7/
1991 Sequester				-15,000
1992	1,209,924,000	1,202,398,000	1,190,396,000	1,188,593,000 8/
1993	1,245,396,000	1,228,455,000	1,228,455,000	1,214,793,000 9/
1994	1,198,402,000	1,277,880,000	1,277,880,000	1,277,880,000
1995 10/	1,266,961,000	1,259,590,000	1,259,590,000	1,258,472,000 11/
1995 Rescission				-1,098,000
1996	1,279,096,000 10/	1,355,866,000	1,263,189,000 10/	1,355,866,000 12/
1997 10/	1,320,555,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research consolidated at the Secretary's level.

3/ Excludes funds for AIDS research and education (\$39,032,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ The 1990 request excludes funds for the National HIV program (\$42,651,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

- 5/ Excludes enacted administrative reduction of \$3,740,000.
- 6/ Excludes \$44,476,000 in NRSA training programs not considered.
- 7/ Excludes Section 514 reductions of \$31,708,000.
- 8/ Excludes Section 214 and 513 reductions of \$9,398,000 and enacted rescission of \$1,407,000.
- 9/ Excludes Section 215, 511, and 513 reductions of \$13,662,000.
- 10/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
- 11/ Excludes procurement reform, rent, and salary and expense reductions of \$1,118,000.
- 12/ A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92, and P.L. 104-99.

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National Heart, Lung, and Blood Institute

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	14	13	13
Office of Program Planning and Evaluation.....	43	41	41
Office of Prevention, Education and Control.....	34	34	34
Office of Administrative Management.....	47	42	42
Division of Heart and Vascular Diseases.....	64	65	65
Division of Epidemiology and Clinical Applications.....	78	76	76
Division of Lung Diseases.....	28	30	30
Division of Blood Diseases and Resources.....	30	30	30
Division of Intramural Research.....	376	373	373
Division of Extramural Affairs.....	114	109	109
National Center on Sleep Disorders Research.....	2	2	2
Total, NHLBI.....	830	815	815

Average GS/GM Grade

1991.....	10.04
1992.....	10.05
1993.....	10.03
1994.....	10.46
1995.....	10.42
1996.....	10.30
1997.....	10.00

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Detail of Permanent Positions

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Executive Level I	0	0	0
Executive Level II	0	0	0
Executive Level III	0	0	0
Executive Level IV	0	0	0
Executive Level V	0	0	0
Subtotal	0	0	0
Total Executive Level Salaries	0	0	0
ES-6	3	3	3
ES-5	2	2	2
ES-4	11	11	11
ES-3	0	0	0
ES-2	0	0	0
ES-1	3	3	3
Subtotal	19	19	19
Total ES Salaries	\$2,029,700	\$2,115,000	\$2,147,000
GS/GM-15	68	67	67
GS/GM-14	82	82	82
GS/GM-13	74	73	73
GS-12	64	63	63
GS-11	81	81	81
GS-10	10	9	9
GS-09	43	43	43
GS-08	49	48	48
GS-07	98	98	98
GS-06	19	19	19
GS-05	21	21	21
GS-04	25	25	25
GS-03	10	10	10
GS-02	3	3	3
GS-01	2	2	2
Subtotal	649	644	644

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	1995 Actual	1996 Estimate	1997 Estimate
Grades established by Act of July 1, 1994 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	26	26	26
Senior Grade	16	16	16
Full Grade	13	13	13
Senior Assistant Grade	4	4	4
Subtotal	60	60	60
Ungraded	116	114	114
Total positions, end of year	844	837	837
Total FTE, end of year	830	815	815
Average ES level	4	4	4
Average ES salary	\$106,826	\$109,539	\$112,825
Average GS/GM grade	10.42	10.30	10.00
Average GS/GM salary	\$45,672	\$46,832	\$48,237

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FRIDAY, APRIL 19, 1996.

NATIONAL EYE INSTITUTE

WITNESSES

DR. CARL KUPFER, M.D., DIRECTOR, NATIONAL EYE INSTITUTE

DR. JACK A. McLAUGHLIN, M.D., ASSOCIATE DIRECTOR FOR EXTRAMURAL RESEARCH

ED McMANUS, DEPUTY DIRECTOR

CAROL LIPSON FIVOZINSKY, BUDGET OFFICER

DR. HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We now continue our hearings for the National Institutes of Health, with the National Eye Institute. And we're very pleased to welcome Dr. Carl Kupfer, the Director of the NEI. Dr. Kupfer, why don't you also introduce the people who are with you and then proceed.

INTRODUCTION OF WITNESSES

Dr. KUPFER. Thank you, Mr. Chairman.

On my far left is Ms. Carol Fivozinsky, who is our Budget Officer. On my immediate left is Mr. Ed McManus, the Deputy Director. On my right is Dr. Jack McLaughlin, who is the Associate Director for Extramural Research. Of course, Dr. Varmus and Mr. Williams.

OPENING STATEMENT

Mr. Chairman, I would like to discuss a very common condition that affects 25 percent of all adult Americans, myopia or nearsightedness. This is something that has been of interest for many, many people during the last few years. Over the last 15 years it has become very clear for the first time, after very extensive laboratory research and extensive studies of patients, that the controversy between the genetic basis for nearsightedness and the impact of environmental conditions has been resolved. It seems to come down that there is a small genetic predisposition, but the main factor seems to be environmental in nature.

And in a sense, this is good news, because one can manipulate environmental factors much more easily than genetic factors.

In short, it appears that the cause of myopia is the fact that objects that children look at are focused in back of the eye on the retina—the eye being like a camera. Whatever is being focused must fall on the film, or the retina. If the object of regard falls behind

the retina, the eye, trying to compensate, begins to grow longer and longer to catch up with where the image is in focus.

If this is correct, as the working hypothesis, we should be able to enable the child who is beginning to develop myopia to focus those images clearly on the retina by the appropriate optical correction, not just glasses, but special types of glasses. And hence, we will begin in the next few months a clinical trial to determine whether in point of fact we can prevent or significantly slow down the development of myopia.

I would like to mention two clinical trials that have been completed recently. The first deals with the population receiving cataract surgery. A very small number, about 5,000 a year, do develop a very severe infection following the cataract surgery. We have been able to demonstrate that in the vast majority of these patients a simple injection of antibiotics into the eye that's infected can control the infection completely. It is not necessary to do the very expensive operation called vitrectomy, and it is not necessary to give systemic corticosteroids. The amount of money saved by not having to do these very extensive procedures is about \$40 million a year.

A second clinical trial dealt with retinopathy of prematurity, affecting very premature infants. We now have a follow up of a study that began about eight years ago that shows that we can reduce blindness in these infants by 25 percent on the basis of their measured vision. Now they are about 5½ to 6 years of age.

This saves about \$38 million to \$65 million a year, but I would like to stress that whenever one does an economic analysis, one has to think about those aspects of life on which we cannot place a price tag. And that is the quality of life. If we can save an infant at birth from becoming blind, that means for a period of 70 or 80 years, that individual will be able to enjoy a far superior quality of life.

Finally, I would like to call your attention to the fact that the NIH clinical center has served us very well in the ability to rapidly translate from the laboratory to the clinic, research findings that then result in small but effective clinical trials. We've done two clinical trials dealing with AIDS patients. One was the demonstration that a drug called Foscarnet was effective in not only preventing the spread of cytomegalovirus retinitis, but actually increasing the life expectancy of the patient.

The second, more recent, was the major change in the treatment of CMV retinitis by inserting into the back of the eye an implant containing ganciclovir, one of the anti-CMV drugs. This has completely revolutionized the treatment, because now one does not have to depend on long-term intravenous therapy. One can place such an implant in the eye and maintain good control of the infection for an eight month period and then replace that implant with another one.

Again, the quality of life aspects are as important or perhaps even more important than the actual benefits derived from these simple treatments.

Mr. Chairman, in fiscal year 1997, the budget request for the National Eye Institute is \$310,072,000. I'd be happy to answer any questions.

[The prepared statement and biography of Dr. Carl Kupfer follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Eye Institute

Mr. Chairman, I am pleased to provide an overview of the National Eye Institute's recent advances, and to describe several of our important research challenges. I will highlight how NEI research contributes to prevention of vision loss from eye diseases and disorders, thus maintaining a better quality of life and reducing costs for our nation.

One of the most promising areas of NEI research has to do with myopia, or nearsightedness, which affects at least 25 percent of U.S. adults. Developing a means of safely preventing myopia will spare millions of Americans from a vision problem that will need correction throughout life.

We are not born with normal vision; we develop it. Within the second or third year of life, the eye grows in length, and muscles that control its power to focus light develop further. NEI-supported investigators confirmed a hypothesis that eye development is regulated by visual feedback in animal experiments. This information will be useful for developing myopia-prevention strategies that can be tested in clinical trials with humans in the future.

Despite myopia's enormous cost to society, we know very little about how the condition develops and how it runs its course in humans. Most people who have myopia develop it between the ages of 6 and 14. No longitudinal study had ever been conducted on the parts of the eye involved in focusing of light, an important component of vision, during those crucial early years of growth. Today, technology makes such a study safe and feasible using human subjects. The NEI is continuing its support of the Orinda Longitudinal Study of Myopia to identify risk factors for myopia in schoolchildren. The long-term objective of this study is to find out why a particular child becomes myopic, identify risk factors for myopia, and gain clues as to how we can prevent myopia from developing.

In addition to research on myopia, the NEI also has supported investigation of a condition prevalent among the youngest of young Americans — premature infants. In 1995, long-term results from an NEI-supported clinical trial demonstrated the value and safety of using cryotherapy, a retinal freezing technique, to prevent blindness in premature infants who have a condition called retinopathy of prematurity. This condition causes vision loss in more than 3,000 low birthweight infants born in the United States each year. A 5-1/2-year followup of children in the NEI-supported Cryotherapy for Retinopathy of Prematurity study showed that eyes treated with the procedure were much less likely to become blind.

The NEI not only helps Americans begin their lives with good vision, but also makes the eye health of older Americans a priority. Cataract is a condition that affects many older Americans. In 1995, results of an NEI-supported clinical trial indicated that patients who develop a bacterial infection following cataract surgery need not undergo vitrectomy, a costly surgical procedure to replace the gel-like filling inside the eye. The infection, called endophthalmitis, occurs in approximately 5,000 to 6,000 of the 1.35 million people who have cataract surgery each year, and can lead to blindness. The Endophthalmitis Vitrectomy Study (EVS) also found that giving patients antibiotics to treat the infection directly at the infection site works just as well as giving antibiotics intravenously.

The EVS results will mean fewer surgeries and shorter hospital stays, or no hospital stays, for many people each year. To help ensure that these findings were quickly put into practice for immediate public health benefit, the NEI sent a clinical alert to more than 15,500 ophthalmologists nationwide. Full implementation of the recommendations from this trial can potentially save the nation at least \$40 million dollars in health care costs annually. The EVS results will create a positive economic benefit for the nation for years to come, as the enormous burden of cataracts will increase significantly in coming decades as the American population ages. Decreasing the cost of cataract management will provide significant savings in Medicare reimbursement for this condition, which reached 12 percent of the entire Medicare Part B budget in the early 1990s.

For working-age Americans, diabetic retinopathy is the leading cause of blindness. The 16 million Americans who have diabetes are at risk for this disease. When diabetic retinopathy is detected in time, it can be treated very successfully with laser surgery, and vision loss can be prevented. The benefits of laser surgery were demonstrated in a landmark series of NEI-supported clinical trials. Treatment of diabetic retinopathy now saves society between \$1.2 and \$1.6 billion dollars per year, primarily by reducing the lost productivity blindness causes. NEI-supported investigation continues to study how diabetic retinopathy develops, with the ultimate goal of discovering interventions that will prevent it. We are moving closer to understanding how to prevent the condition pharmacologically. Studies have shown that a substance called vascular endothelial growth factor (VEGF) is present in dramatically elevated levels in the eyes of people who have diabetic retinopathy. Recent NEI research indicates that treating primates with a biological substance that blocks VEGF suppresses development of abnormal vessels in the eye that leads to the condition. This exciting result opens the possibility that someday we will be able to develop a pharmacologic means to prevent diabetic retinopathy.

Because laser surgery is most effective when diabetic retinopathy is treated in a timely manner, we must educate people about the importance of having a yearly dilated eye exam to detect the disease in its early stages. This sight-saving message is one of the themes of the National Eye Health Education Program (NEHEP), which has made significant progress toward reaching the 16 million Americans with diabetes. The NEHEP staff worked with the American Diabetes Association and 14 other organizations to increase awareness during National Diabetes Month, an event held each November.

Research has shown that diabetes is especially prevalent among the nation's Hispanic population, the fastest growing ethnic minority in the United States. The rate of diabetes among this group is staggering. One in 10 adult Hispanics nationwide has diabetes, putting more than 1.8 million at high risk for diabetic eye disease. To educate this audience about the importance of the early detection and timely treatment of this condition, the *Ojo con su Vision -- Watch Out for Your Vision --* program was launched. The program has reached more than 47 million people in the Hispanic community since it began in October, 1995.

Surveys report that Americans fear loss of vision more than any other disability. Much of the research being conducted on vision is related to issues that, while not life-threatening, have a major impact on quality of life. Improving the quality of life for people with AIDS continues to be an important area of NEI research. Investigators involved in Studies of the Ocular Complications of AIDS (SOCA) are currently working to identify more effective, more convenient, and less toxic therapies for AIDS complications. Twenty-five to 30 percent of people with AIDS develop retinitis due to secondary infection with cytomegalovirus (CMV). Among this population, CMV retinitis is the most frequent cause of visual loss. In 1995, SOCA investigators reported that a combination of two antiviral drugs, ganciclovir and foscarnet, is more effective than either drug alone for controlling recurrence of CMV retinitis.

Another SOCA trial shows that a new drug, HPMPC, significantly slowed the progression of CMV retinitis, and was more convenient to administer than drugs now available. Because preliminary findings in the HPMPC Peripheral CMV Retinitis trial showed the drug to be effective, patient recruitment was stopped. Patients assigned to deferral of treatment who had not yet experienced disease progression were offered HPMPC. Followup for all patients will continue for six months. HPMPC is now the subject of a New Drug Application to the U.S. Food and Drug Administration that requests marketing approval in the United States for treatment of CMV retinitis in people with AIDS.

The NEI intramural program serves as a model for the integration of basic and clinical vision research; concentrates on areas that are not addressed by the extramural program; provides for funds to be quickly redirected to address important health problems; and allows for clinical researchers and basic scientists from a varied array of disciplines to work together on one campus. The Warren Grant Magnuson Clinical Center is a highly specialized patient care facility designed specifically to apply the findings from laboratory research to treatments for diseases, and is a critical component of the NEI intramural program. In 1995, NEI intramural investigators completed their analysis of the ganciclovir implant, a drug-releasing device recently approved by the FDA for use in people with AIDS who have CMV retinitis. This implant was developed collaboratively by intramural and extramural researchers, and has implications for treating other ocular diseases. The NEI researchers who developed this implant are now investigating the use of protease inhibitors, which have raised the immune response in AIDS patients in a clinical trial. If this study is successful, it may be possible to delay or prevent the development of CMV retinitis in people with AIDS.

Looking toward the 21st century, NEI is positioned to make several important advances. One of the most promising is the development of a medical treatment to slow cataract formation. A 10-year delay in the development of cataracts would reduce by nearly one-half the number of people who need surgery for cataract removal, which currently stands at 1.5 million annually. We are laying the groundwork for applying gene therapy to the treatment of potentially blinding retinal degenerations, such as retinitis pigmentosa, a condition that affects 100,000 Americans. Scientists have isolated a defective gene that causes several forms of retinal degeneration, and have brought us closer to learning how to replace the defective gene with a normal gene. This promising new area of research may be a major hope for the treatment of several diseases that cause vision loss.

The NEI supports more than 80 percent of the important basic research that is being done on the human visual system in health and disease today. Research supported by the NEI has a strong impact on commercial activity and is a foundation for development of drugs, devices, and biotechnologies. Forty percent of the research papers provided as documentation for more than 8,000 eye-related patents issued since 1975 cited the NEI or other NIH support. This diverse patent portfolio includes everything from eyeglasses to high-technology surgical instruments. Investment in vision research provides practitioners with information that improves patient care and lowers costs, and provides Americans with information they can use to protect their eyesight. The NEI is also a valuable resource for ensuring that the nation will retain preeminence in vision research in the future.

Mr. Chairman, the FY 1997 budget request for the National Eye Institute is \$310,072,000. I will gladly answer any questions you may have.

CARL KUPFER, M.D., Director, National Eye Institute
February 9, 1928. New York, New York.

Education: A.B., Yale Univ., 1945-48. M.D., The Johns Hopkins Medical School, 1952
Certified. American Board of Ophthalmology, 1958.

Professional History: Internship and Assistant Residency, Wilmer Eye Inst., Johns Hopkins (JH) Hospital, 1952-54. Lab. Asst., Biostat., JH School of Medicine, 1953-58. Research Fellow in Ophth., Harvard Medical School, 1958-60. Instructor in Ophthalmology, Harvard Medical School, 1960-62. Assistant Professor of Ophthalmology, Harvard Medical School, 1962-66. Prof. and Chairman in Ophth., Univ. of Washington School of Medicine; Research Affiliate, Univ. of Washington Primate Ctr., 1966-70. Director, National Eye Institute, 1970-present. Acting Deputy Director for Intramural Research, NIH, 1991-1992.

Professional Organizations: Am. Physiological Society; Assoc. for Research in Vision and Ophth.; Am. Academy of Ophthalmology; Am. Ophthalmological Society; Pan Am. Ophth. Society; Johns Hopkins Univ. Soc. of Scholars; Member, Inst. of Medicine, National Academy of Sciences; Member, Academia Ophthalmologica Internationalis.

Honors and Awards: The Secretary's Special Citation, DHEW, 1972; The Superior Service Award, DHEW, 1974; Presidential Rank Award of Meritorious Executives, 1983; Migel Medal, Amer. Foundation for the Blind, 1976; Public Service Award in Ophth., Amer. Academy of Ophth. and Otolaryngology, 1977; Special Award of Honor, The Assn. for Research in Vision and Ophthalmology (ARVO), 1983; David Rumbough Memorial Scientific Award, JDF, 1983; The Lighthouse Pisart Vision Award, 1984; Cavera Medal of Univ. of Rome, 1985; The Mildred Weisenfeld Award for Excellence in Ophth. 1987; Presidential Distinguished Rank Award, 1991; Statesmanship Award, Joint Commission on Allied Health Personnel in Ophthalmology, 1991; Lions Clubs Intl. Humanitarian Award, 1992; Kupfer Award of the ARVO, 1993; Leadership Award, AOS, 1993; Benjamin F. Boyd Humanitarian Award of the Pan-Am. Assn. of Ophthalmology, 1993; Joslin Diabetes Center-MediSense Award, 1994; RP Humanitarian Award, 1994; Gold Jose Rizal Medal, 15th Asia-Pacific Academy of Ophthalmology Congress, 1995; Person of Vision Award, Prevent Blindness America, 1995.

Other Scientific Activities: Editorial Board, Investigative Ophth., 1969-1977; Editorial Board, Am. Journal of Ophth., 1971-1983; Member, Scientific Advisory Committee, Fight for Sight, 1971-present; Member, National Diabetes Advisory Board, 1976-present.

International Appointments: Member, Board of Trustees, HKI, Inc., 1975-present; Member, Intl. Vitamin A Consultative Group, WHO, 1973-present; Member, WHO Advisory Group for Prevention of Blindness Prog., 1978-1984; Consultant, Pan Am. Health Organization, 1978-present; Coordinator for USA, Priority Area "Eye Diseases," U.S.-U.S.S.R. Prog. for Health Cooperation, 1978-present; Member, WHO Expert Advisory Panel on Trachoma and Prevention of Blindness, 1979-present; Dir., WHO Collaborating Ctr. for the Prevention of Blindness, National Eye Inst., Bethesda, MD, 1979-present; Pres., Intl. Agency for the Prevention of Blindness, October 1982-1990. Consultant in India for the World Bank, 1992-present.

RATE OF GROWTH

Mr. PORTER. I think I'll start with the same question I asked Dr. Lenfant. And that is, your Institute is not increasing at the same rate as others. What are your thoughts or feelings about that?

Dr. KUPFER. I was thinking of what my answer would be when you asked Dr. Lenfant.

Mr. PORTER. I assumed you were, and I didn't want it to go to waste. [Laughter.]

Dr. KUPFER. Well, first, I would say that as Dr. Varmus touched upon yesterday, and as I think we all are beginning to see more and more clearly, even though our institutes are compartmentalized, our research is not. Just to give you one example, about five or six years ago, NEI supported investigators looking at a very rare tumor called retinoblastoma. They came upon the discovery that there are genes which, while present, prevent cancers from forming, but when they are lost, cancer will then form. They're called suppressor genes. They suppress cancer while they're present.

This was an entirely new concept, and has bearing now not only on the retinoblastoma, the eye tumor, but on tumors elsewhere. And this has opened up a whole new field of cancer biology. I'm sure the people doing the study on the eye tumor did not realize where this would lead. So in a sense, I don't think that one should be so concerned about the level of support per institute. I am more concerned with the level of support of biomedical research in total. And that means the support of the National Institutes of Health. There are just too many examples of where activities in one area impinge upon diseases in another.

Obviously, every institute, including the Eye Institute, can list research opportunities. And of course, that is the critical question, the matching of the need to the opportunity. I think again this has been stressed. And as long as we feel that the major needs in which there are research opportunities, are being supported, I think that's the criterion. But again, one has to realize that a rising tide lifts all ships. And I think support of the NIH is our major interest.

Dr. VARMUS. Can I make one brief comment?

Mr. PORTER. Yes.

Dr. VARMUS. I want to applaud Dr. Kupfer's answer and I want to add one or two other things. I realize that this line of questioning could be appropriately applied to all the institutes, or most of them. I feel we're looking at extremely small differences when we pose this question, that there are really very few institutes that deviate from others by more than a half a percentage point with respect to the rise.

I think it's important that we not simply dwell on the increase in each fiscal year as a mark of the commitment to that area of research. I was struck yesterday by Mrs. Lowey's comments about the amount of the increase for breast cancer, as opposed to the amount we've already devoted, due to very rapid increases over the previous two years.

We cannot sustain such increases in perpetuity, because we simply have a limited pot to draw from. If we're going to generate new

initiatives in each year, other institutes will have to be slightly below the average. But no one is being excessively penalized, and the differences that we're looking at are extremely small.

FY 1997 BUDGET LEVEL

Mr. PORTER. I think I'm going to add something right now about the budget level for this coming fiscal year. Because I've gotten very concerned in the last few days that the White House is insisting on changes in the overall funding of programs out of this subcommittee's jurisdiction that will make commitments that are very likely going to be very, very hard to meet under any possible 602(b) allocation.

So I think, I'm trying to send a message to the Administration through you that they have to look more broadly at the entire picture. And while we share their concern about certain programs, this kind of approach is going to tie up our budget in such a way that we're not going to be able to do the things that we want to do.

And our job is obviously to choose priorities and to support those that are the highest. And my worry is that there is too much of the political weight being put on this and not enough intellectual weight that I think is required. I just wanted to say that for the record.

MYOPIA

Going back to myopia, which I think has got to be, you know, we talk a lot about death rates and morbidity and the like, but talking about the quality of life is also important. And I'm surprised that the 25 percent figure is as low as it is. I would have said it's 33 percent or maybe even higher. You didn't say what causes the environmental problem. In other words, why do children have the images focusing behind the retina? Is it simply the development of the skull or what?

Dr. KUPFER. Well, studies have demonstrated that as the eye develops—of course, at birth it is relatively small—it increases in its overall diameter and size. And that increase apparently is coordinated by the focusing of the eye on what the infant looks at. If the image is focused on the retina, the eye will stay the same size.

But if the image tends to be focused in back of the retina, as the child begins to look at things much more closely, then the eye tends to grow. And there is a very nice balance between the amount of visual activity that the infant or very, very young child is involved in and the growth of the eye. And then at some point, that process stops and the eye is of the right size.

Now, it appears that there are some infants who have probably some genetic predisposition in which the ability to keep the focus of an object on the retina is decreased. They keep under-correcting the image, so that it continually falls in back of the retina. And that is the stimulus for the eye to continue to grow.

Now, if we can improve those children's ability—and we will identify those children, because we will be taking children who already have very slight amounts of myopia—to keep that image right on the retina, then we hope to prevent the continual increase

in the size of the eye, and therefore prevent the common form of myopia.

Mr. PORTER. So you would do this with devices that would be the opposite of the kind of corrective devices that you would use later? In other words, you would put glasses upon a child if you're going to use glasses, that would be, not a correction for nearsightedness, but a correction for farsightedness? Is that right? Or is that correct?

Dr. KUPFER. Well, it's going to be——

Mr. PORTER. In other words, the correction would be the other way around, to reverse the process.

Dr. KUPFER. Right. Well, actually, it's sort of just in between those two alternatives. Because it will be a glass that changes the ability of the eye to focus light continuously through the entire range of the lens, so that the child will always be able to choose that portion of the lens to look through, that focuses the light directly on the retina.

Now, we have a lot of experience with this particular lens, because very often, individuals in their late 40s, 50s, 60s, who need bifocals, prefer to have this multi——

Mr. PORTER. Which is a Varilux, right?

Dr. KUPFER. That's right, exactly, sir. And they prefer to have this, because they can look through different portions of the lens for different distances. And there is evidence to suggest that fitting a child who appears to be on the road to developing myopia with such a glass will slow down or prevent that development. We will do the study to determine this.

CATARACT DRUGS

Mr. PORTER. That is fascinating.

You set a goal of delaying the development of cataracts by 10 years, which would reduce the number of cataract surgeries by nearly half. Are there any drugs in the testing pipeline which would slow the development of cataracts to make this goal possible?

Dr. KUPFER. A number of drugs have been used in laboratory models of cataract. Unfortunately, these drugs are either too toxic or have great difficulty in getting into the lens. So at the present time, the development of such drugs are underway.

What I think is equally important is that we are learning more about the possible mechanism for the development of cataract. And if we understood the mechanism better, then the type of drug that would be designed might be somewhat different. So I think there must go hand-in-hand continued basic research, molecular biology, of cataract formation and understanding of what types of drugs to develop.

AGE-RELATED EYE DISEASES

Mr. PORTER. It is projected that the number of blind persons will double in the next generation, related to the aging of the population, with the major causes being glaucoma, macular degeneration and cataracts. Do we know much about the cellular processes that cause these conditions, and are retinal cell transplantation

and regeneration on the rise as realistic options to deal with these diseases?

Dr. KUPFER. Well, perhaps I could take them one at a time. There are four major eye diseases that are age-related, that is, as the population ages, the prevalence of these eye diseases increases. And they are diabetic retinopathy, cataract, glaucoma and macular degeneration.

DIABETIC RETINOPATHY

Now, in diabetic retinopathy, we've made some very major strides. In fact, as a result of three clinical trials done over the last 15, 20 years, we can now assure a diabetic that they have less than a 2 to 3 percent chance of going blind if they continue to be seen by an eye care practitioner and receive the types of interventions, mainly laser treatment, that we have found to be effective. So we've been able to control the development of blindness and prevent the development of blindness in diabetic retinopathy.

What we would like to do is have a more primary prevention. This year, there have been some very interesting developments in a constituent of the cells that line the blood vessels, the endothelial cells. These cells produce a factor called the vascular endothelial growth factor, that appears to cause growth of blood vessels that is not controlled. And this is the hallmark of diabetic retinopathy. The blood vessels, instead of being within the retina, begin to proliferate, and grow out into the back of the eye. They're very friable, fragile, they bleed, and the hemorrhage fills the eye.

In addition to finding this factor, we now know how to prevent this factor from causing proliferation of vessels. I think the stage is now set so that within the next two or three or four years we may see this type of treatment applied to diabetic retinopathy patients who are just beginning to get into trouble. Perhaps we can prevent the development of retinopathy and hence, blindness, by very early preventive measures.

So I think there is every reason to believe that diabetic retinopathy will not increase in the future, if we can develop further treatments, but even more importantly, ensure the treatments we now have are available to the diabetic population. Amazingly enough, only 50 percent of Americans who would profit from laser treatment of their diabetic retinopathy actually receive this treatment. We don't know why this is, but we are doing research now to try to determine what the barriers are that prevent these individuals from receiving treatment.

CATARACT

As far as cataract is concerned, again, as I had mentioned, we are looking at mechanisms. One of the mechanisms that seems to be most pertinent to the development of opacities in the lens is the fact that as you might imagine, for the lens to stay absolutely transparent, it must have a uniform index of refraction. That is, there should be nothing in the lens that causes light to bounce about or be reflected. The lens is superbly constructed to do this.

Apparently what happens in early lens opacities is that there is a redistribution of fluid in the lens, so that some parts of the cells in the lens have too much protein and others have very little pro-

tein. These changes in concentrations of proteins begin to cause changes in the way that light passes through the lens and causes opacities. This is what is called phase separation, the separation of the proteins in the fluids.

Now, if this proves to be the case, and we are pursuing this very aggressively, then there are ways of preventing this phase separation. So again, if we can really reduce the number of, the progression of cataract, as we say, by 10 years, we will bring this under major control.

GLAUCOMA

In the case of glaucoma, I think there have been some very major developments in the last year or two, and we are now beginning to identify the genes that control the onset of elevated intraocular pressure. There are two types of glaucoma that have really begun to give us molecular genetics information.

The first affects very young people and occurs in families and is a dominantly inherited condition. We know now where the gene is, and we're trying to focus down and clone the gene. The second is, of course, the more common form of what is called open angle glaucoma. This accounts for about 80 percent of all glaucoma. We now have several very good groups working on trying to identify the gene in this situation.

There's also a new hypothesis in glaucoma, and that is the production of a toxin by the cells of the retina, which appears to cause these cells to degenerate. And that is being actively pursued. So, I think there are very good indications that glaucoma in the next decade is going to be brought more under control.

MACULAR DEGENERATION

Finally, macular degeneration, which is the major cause of new adult blindness. Here we are looking very carefully at the molecular biology of the cells in the retina that receive the light and convert that light to electrical impulses. There are studies underway in retinal cell transplantation. As you well know, Mr. Chairman, one of the problems with transplanting cells is ensuring they will not be rejected.

So one of the first exercises that is being conducted is to take cells from the retina and treat them in such a way that their surface antigens, the things that stimulate the reaction, are blocked; and therefore, transplanting such tissue will be done without rejection.

But even more important, the question is whether such transplantation will be able to rescue the cells that are degenerating. Those studies are beginning, first in transgenic mice in whom we can simulate these retinal regenerations, and at the appropriate time, in patients.

So I think that it is true, if nothing were done, that blindness prevalence would double in the next 15, 20 years. But I think we are well on our way to bringing these things under some form of control.

LASERS FOR MACULAR DEGENERATION

Mr. PORTER. That was a perfect answer to the question.

My next question dealt also with macular degeneration and your testimony before the Senate authorizing committee. And I guess what the question would be is the role of laser surgery in ultimately stopping that degeneration before it does damage. Is that what you're hinting at?

Dr. KUPFER. Well, the laser has been used in one form of macular degeneration. There are two forms of macular degeneration.

The most common form is what is referred to as a dry type in which certain cells of the retina just begin to degenerate and die. One sees a widespread death of these cells in the area that provides the sharpest central vision. This accounts for about 90 percent of all the macular degeneration, but only accounts for about 10 percent of the blindness. These people have major disability, but they're not blind in the sense of the legal definition.

The wet type, in which there is actually proliferation of blood vessels and hemorrhage, and destruction of the macula, is the less common type, but it accounts for 90 percent of the blindness. And that is the type that we can treat with laser. This is a proliferation of new vessels. By placing the laser on these vessels, we can destroy them.

The problem is, that if the new vessels are right smack in the center of the macula, and we try to remove them, we will destroy the macula as well as the vessels. So we must come up with other therapies. And again, going back to this vascular endothelial growth factor that seems to be the stimulus for causing blood vessels to grow. There may be ways of medically treating these cases to prevent the blood vessels from growing and resulting in the loss of vision. So that will be the direction of our research activity.

BIOLOGY OF BRAIN DISORDERS

Mr. PORTER. Part of the increase in your budget request is associated with the NIH special emphasis area of biology of brain disorders. Can you tell us what elements of eye disease research fit into this special emphasis area?

Dr. KUPFER. The eye is actually part of the brain. The optic nerve is a nerve track to the brain, the retina is very similar in construction to the brain. And it offers certain advantages, because the retina is a very nicely layered structure, and one can correlate function with morphology on that basis.

But even more important, the visual system is perhaps the best system in which to study brain function because we can measure the stimulus very accurately. After all, it's light and you can measure light physically. We can measure the output of the visual system in terms of eye movements. If we see something to our left, we turn our eyes to look at it.

And therefore, in both patients and normal subjects and trained animal subjects, one can study the visual system and learn how the brain functions. What we learn from the visual system will be generalizable and translatable to all the other parts of the brain. So in that sense, the visual system offers some unique advantages.

Just to give you one example, again, where there is interdisciplinary activity, one of our grantees several years ago was very interested in trying to determine how to bring about regeneration in the optic nerve. And since the optic nerve is part of the brain, it, like other parts of the brain, will not regenerate after birth. But he decided to do his experiments on the spinal cord. This was one of the first indications that with certain types of manipulations, one could keep the spinal cord intact after a crushing injury.

Now, why he did it on the spinal cord, not the optic nerve, I think, is just a question of convenience. The spinal cord and the optic nerve are quite similar in terms of their reactions. But here's an example of where an eye researcher chose the spinal cord to do work and this opened up the whole field with other researchers of spinal cord injury treatment.

The research going on in retina has a direct bearing on research in the brain. One more example. There is a group of cells in the retina that produces a growth factor. It's a growth factor in the sense of not causing cells to proliferate, but maintaining the health of the cells for a longer period of time. It turns out that this has one of its greatest effects in cells in the brain, in the cerebellum, which controls our balance. And it may be that this growth factor, found in the retina, may be of great value in some of the central nervous system diseases.

GLAUCOMA TREATMENT

Mr. PORTER. Your clinical trial on the use of laser for glaucoma seems to affirmatively answer the question of whether early laser treatment is better than eye drops. How widely translated into clinical practice is this finding?

Dr. KUPFER. I think that the study equated laser with eye drops in the sense that they were alternative therapies that seemed to be comparable in preserving visual function and keeping intraocular pressure under control. I think the determination as to whether drops are used first or the laser is used first is a discussion that is held between the ophthalmologist and the patient.

Because as you may imagine, some patients who would be in their early 60s may decide that they would like laser and then would not have to be concerned about taking drops for four or five or six or more years. Other patients in their 80s may say, well, look, I don't want to have a laser treatment, I don't mind putting a drop once or twice a day in my eye. I have lots of time on my hands and there's no problem. So I think it's an individual decision.

But I think the value of the study is that it gives the ophthalmologist another way of controlling the pressure in the eye, and opens up further flexibility in treatment patterns.

Mr. PORTER. Does any of this bear on the cost of the alternatives, laser as opposed to eye drops?

Dr. KUPFER. Actually, it's almost a wash. Because in general, starting with laser delays the need for eye drops by three or four or five years. And over that period of time, the cost of the eye drops just about equals the cost of the laser treatment and the follow up.

But there is another study that we are supporting which might even be of greater impact, and that is, surgery versus medical treatment. The importance of this is that there is preliminary data

from the U.K., United Kingdom, that initial surgery controls the pressure for a much longer period of time, requiring no drops, and is much more effective even than the laser.

So we are doing a study now to make this comparison. And in addition, within the study, we are measuring quality of life. Because as you can imagine, individuals will want to comment on what this choice of intervention has meant to them, having surgery versus taking drops. And that information may be even more valuable than what we as ophthalmologists say, well, the pressure was controlled and the visual function maintained.

We are now realizing that we have to understand the impact of what we do from the patient's perspective. And that's where our measurement of quality of life and visual function comes in. We've been working for two years on such a way of measuring quality of life and visual function, and as a matter of fact, this Sunday morning, at our yearly meeting of all the vision researchers, we will be unveiling this mechanism. We hope it will be very rapidly picked up and used in our clinical trials, as well as in practice.

CLINICAL RESEARCH

Mr. PORTER. In your testimony, you describe the importance of the NIH clinical center to your intramural clinical research program. Is ocular disease clinical research conducted broadly in the extramural community, or is the NIH clinical center a major center for this activity?

Dr. KUPFER. I think that the amount of clinical—first of all, let me say, Mr. Chairman, that we have always, always supported a considerable amount of clinical research in the community through our clinical trials program. This represents 10 percent of our budget, and we feel that without clinical trials, we will never be able to provide a scientific base to the practice of medicine in general and ophthalmology in particular. So that in terms of clinical trial activity, a substantial amount is being done in the extramural community.

Having said that, there are certain activities which are better done in the clinical center. And I'll give you two examples. A number of years ago, a drug called cyclosporin first became available. And it had been used in Europe with mixed results. It was very toxic, causing kidney trouble. On the other hand, it seemed to be very beneficial in treating inflammation of the eyes.

Our investigators in the clinical center decided that they would make a major effort to determine as quickly as possible where cyclosporin was of value, how we could make it safer. And over a period of years, with very close collaboration with the company producing cyclosporin, a series of papers delineated what conditions were best helped by cyclosporin, what efforts should be made to prevent toxicity, and very quickly, this data was disseminated to the community. So here was a very unique opportunity where the transfer of research from the laboratory to the clinic could be done very, very quickly.

The second example, which I mentioned in my opening comments, had to do with the AIDS situation. Again, in response to the need for a very rapid turnaround and with the collaboration between the National Institute of Allergy and Infectious Disease and

the National Eye Institute, we mounted two very major clinical trials, conducted them very quickly, and got the results out very quickly. One was the addition of foscarnet as an anti-CMV drug, and the other was the ganciclovir implant into the vitreous.

So in answer to your question, the vast majority of our clinical research is in the extramural community. But there are certain activities that are best done in-house, and they are being done at the present time.

There's one aspect to the clinical center which I think is so critical, and that is, to the best of my knowledge, it may be the only setting where there are a large number of laboratories adjacent to the actual wards where the patients are housed, and the actual clinics where the patients are examined. And that closeness, 25 feet, is absolutely essential. It is amazing, once you begin to separate the laboratory from the clinic, how difficult it is for them to interact.

CMV RETINITIS

Mr. PORTER. The Institute supported a recent clinical trial of a two drug approach to treating recurrent CMV retinitis, which affects up to 40 percent of AIDS patients, and is their most common cause of blindness. Yet this new treatment doesn't sound like a panacea, because of side effects, inconvenience of administering it, and cost. Is CMV retinitis one of the AIDS-related opportunistic infections cited in the Levine Report as needing additional research effort?

Dr. KUPFER. Yes, sir. CMV retinitis is a major opportunistic infection of patients with AIDS. And it is of great interest to us, because it affects the eye and really impacts the quality of life. These patients can become blind very, very rapidly, and the loss of vision can very often make the difference between someone continuing to function in society and being unable to.

I think the studies that have been done in the past of looking at systemically administered drugs and frequent intravenous injections have been overtaken by new forms of therapy. For example, the ganciclovir implant, in which we place this little implant into the vitreous of the eye and then for eight months, the drug is slowly delivered and keeps the infection under control.

That can be combined with oral ganciclovir, and obviously make it much more reasonable for a patient to undergo long term therapy. The combined drugs were done at a time when we wanted to be sure that we were not only controlling the infection, but controlling it for a long period of time. So we took people who failed ganciclovir, who failed foscarnet, combined the two drugs at a higher level, and found that yes, they did prolong good vision. But as you pointed out, the side effects were quite significant.

But fortunately, we've moved past that point, and can now do oral and local treatment.

EFFECT OF ASPIRIN ON DIABETIC RETINOPATHY

Mr. PORTER. Another NEI clinical trial showed that contrary to popular conceptions, the use of aspirin for cardiovascular problems does not exacerbate diabetic retinopathy. Will it be difficult to persuade physicians to change their clinical practice in this area?

Dr. KUPFER. You might remember that people who tend to have a problem with bleeding, whether it's an ulcer or they're on drugs that prevent bleeding, are told not to take aspirin. So the diabetic patient, because they have a tendency to have bleeding in their eye, were told not to take aspirin.

When we did our clinical trial, we tested this situation, and as you pointed out, found that those taking aspirin had no more episodes of hemorrhage than those who were not. I think this is being implemented in the community because aspirin has turned out to be of great value in other conditions, such as preventing cardiovascular disease. And I think that the medical establishment has been very happy to have this reassurance that they can prescribe aspirin to their diabetic patients.

Mr. PORTER. The finding sounds very strange to me, Dr. Kupfer, because you would think logically that the eye or the nose where the blood vessels are probably the closest to the surface, I guess you would say, would tend to bleed more. It didn't happen?

Dr. KUPFER. Well, it took a certain amount of concern to mount this program. And of course, we did it with the agreement of the participating physicians, the patients and of course the data and safety monitoring committee that watched very carefully for any adverse effects. But this was a large study and there were 4,000 patients involved who were randomized to aspirin and no aspirin. So I think we can feel very confident that the results are reliable.

Oh, Mr. McManus reminds me that we have the active cooperation of the Heart, Lung and Blood Institute. It's always good to have a good sized institute standing behind us like that.

NUCLEAR MAGNETIC RESONANCE IMAGING

Mr. PORTER. Your budget justification indicates that nuclear magnetic resonance and magnetic resonance imaging are being increasingly used as research tools for studying ocular diseases. Can you tell us in what situations these tools are most useful?

Dr. KUPFER. At the present time, most of our experience has to do with experimental cataract. One of the problems with treating cataract in patients is that we now have the feeling that if we wait until we can see a lens opacity, it may be too late. So we must develop ways of predicting very early on which patients are going to develop lens opacity.

The nuclear magnetic resonance technique has been shown by our intramural laboratory researchers to demonstrate changes very early in the movement of water. Remember, I had mentioned earlier that there seems to be shifts of water in the lens and shifts of protein concentrations. That may even precede the appearance of opacity. And these shifts can be monitored by this technique.

We are now on the verge of applying it to patients. And there is a center at the clinical center that does this imaging, and we are collaborating with them to begin to examine very early lens changes in patients, and see if we can predict who's going to go on to cataract and who will not.

CONTACT LENSES

Mr. PORTER. I haven't asked this question for a few years, so I'd like to ask it again. Long term studies of effects of the use of contact lenses, do they show any long term problems?

Dr. KUPFER. There are two aspects of the contact lens story. The first has to do with the individual who wears hard contact lenses. And there is some evidence now to suggest that after 15 or 20 years, there are changes in the cells that line the interior of the cornea that probably indicate some low level of damage. And I think we are seeing more and more people moving from hard contact lenses to soft.

The problem with soft lenses is that they are so comfortable and patients feel that they are so benign that they are left in, despite the fact that they are often told to take them out every night. They are left in for days on end. And the problem has presented that if one has a speck of dust underneath the lens and that speck of dust irritates the cornea, it can become infected. We are seeing a number of very severe infections in patients who are wearing soft lenses and perhaps not following the directions that they should.

The ultimate answer would be to develop a contact lens that would be 100 percent permeable to oxygen. And if one could do that, then there probably would be enough oxygen going to the cornea so that even though there might be an irritation, the cornea could control it and not become infected.

So the move in contact lenses is to develop a new class of lens that would allow greater permeability of the oxygen to keep the cornea much healthier. And that is the direction that research is going.

Mr. PORTER. Isn't it correct, though, that as you get a lens that is more oxygen permeable, it is more difficult to correct astigmatism with that kind of lens?

Dr. KUPFER. That is correct. One of the drawbacks on the soft lens is because it is soft it tends to mold to the cornea. And if the cornea is highly astigmatic, then one has a problem. And that is the reason why some people must wear a hard lens.

PUBLIC OUTREACH

Mr. PORTER. As part of your public outreach efforts, you have developed a new school science program for grades 4 to 8. Do you have any data on how widely used the program is, and does the National Science Foundation have similar efforts underway with its extensive science education programs?

Dr. KUPFER. We have distributed 25,000 copies of this brochure, which is geared for a teacher or scientist to go into a school room and have a module to teach how the eye functions. There are also a number of very simple but effective experiments to demonstrate to the school children various aspects of vision.

We are working with the Association for Research in Vision and Ophthalmology, which is the main vision research organization, with a membership of about 8,000 people, and they have taken it upon themselves to recruit their staff to begin to go into schools. And that will go into high gear at the beginning of the next school session in September.

My understanding is that the National Science Foundation does have education programs like this, but the difference is that we are specifically emphasizing vision.

RESEARCH MANAGEMENT AND SUPPORT REDUCTION

Mr. PORTER. Dr. Kupfer, you have the reputation of being one of the best managers at NIH. How are you handling the 7.5 percent reduction in research management and support that was mandated in the 1996 appropriation?

Dr. KUPFER. We've taken a number of steps to respond to that. The first thing that we have done is to not fill certain positions. We do not have an executive officer at the moment, and Mr. McManus is our acting executive officer. We do not have anyone in charge of our international program. We have not replaced that individual. We held off for about six months to replace people in the information office. We have two vacancies in the extramural program, one for a person to be in charge of a program and the other for a program grant specialist that we will not fill.

The National Eye Health Education Program, which we feel very strongly about, is being cut somewhat in its budget to accommodate the decrease. And I think that in general, we have responded to the needs. But I must say that this has been done with great difficulty, because we started out running a very tight ship. And when you try to cut a tight ship, you begin to find that there are gaps in what one can do as effectively, as what one would wish to do.

Mr. PORTER. Dr. Varmus, do you want to comment on this whole area?

Dr. VARMUS. Just to say that, as Dr. Kupfer has emphasized, this is an extremely difficult set of cuts to make. But we are still at risk, of course, for taps from the Department that come from the Research Management and Support pool, maybe as much as 9 percent of our RM&S budget. We don't see those being reduced. In fact, they may be increased as a result of our increased support of the Department's Program Support Center.

Furthermore, we are seeing erosion of some of the components of our RM&S budget that I think are extremely important for maintaining the high quality of the people who do program analysis in each of the institutes. For example, it's difficult for them to travel to meetings. We're having to reduce the number of journals that those folks can receive. If we don't maintain the high scientific quality of our program managers, the ability to manage our programs effectively will decline.

Most institutes, I believe, have been able to absorb these costs, at least for the moment. But they have been able to do so without being able to reduce the number of full time equivalents in those positions, as we would like not to fire anybody. Less than a third of what we have achieved, less than 2.5 percent of the total reduction, has come from reducing things fast, because we don't want to fire anybody. And that's meant that we've had to take the cuts out of activities which are essential to running an effective program.

FISCAL YEAR 1996 REDUCTION PREFERENCES

Mr. PORTER. If you had your choice last year between cutting money for extramural grants or taking this kind of 7.5 percent cut, which would you have chosen?

Dr. VARMUS. I would not have argued that we should take the cuts in grants, by any means. But one of the things I've learned is that every institute has its own way of categorizing what is in RM&S. And for example, some have more contracts than others in RM&S. To give us the flexibility to take those cuts I think would have been justified without taking cuts from the grant pool, which I would not have allowed. I think it would have been possible to perhaps spread the reduction a little more broadly among some of the programs that perhaps could have absorbed the reductions more easily.

Mr. PORTER. As you know, these were reductions that all departments under our jurisdiction made. In other words, everyone had the same reductions, and we did not feel it was fair to not provide the same requirements of NIH. And I know it's been very difficult and painful to do this, but I think it's something we had to ask you to do.

Dr. VARMUS. As long as we don't have an additional directive this year, I think we can manage as well as last year.

Mr. PORTER. Dr. Kupfer, you're the dean of the directors of NIH. One can certainly see why. I sat here as you were giving the answers to the questions, thinking, I'm listening to someone who, the sign of brilliance is to reduce complex things to understandable terms, or one sign, at least. And your answers were absolutely, in my mind, brilliant.

And I enjoyed our discussion and I come away from it as an individual with a lot of learning that I did not have before. And I really appreciate the fine job you're doing at NEI. We are all in your debt. It's obvious that you've made tremendous progress over the years that you've been there. And I'm sure it's been recognized professionally, but we in the Congress would like to recognize it as well.

Dr. KUPFER. Thank you very much, sir.

Mr. PORTER. Thank you, Dr. Varmus.

That concludes our hearings for this morning. We stand in recess until 2:30 on Monday.

[The following questions were submitted to be answered for the record:]

Questions Submitted by the Subcommittee

FY 1995-1997 BUDGET

Mr. Porter: Identify FY 95-97 spending on the following: Retinitis Pigmentosa, Glaucoma, Diabetic Retinopathy, Macular Degeneration, Cataract, and CMV Retinitis.

Dr. Kupfer: The following data identifies the funding for Eye Diseases for FY 95-97 (dollars in thousands):

	<u>Fiscal Year</u>		
	<u>FY 1995</u>	<u>FY 1996</u>	<u>FY 1997</u>
Retinitis Pigmentosa	\$15,870	\$16,651	\$16,917
Glaucoma	28,702	30,226	30,785
Diabetic Retinopathy	15,468	16,229	16,488
Macular Degeneration	68,257	71,615	72,760
Cataract	23,598	24,851	25,310
CMV Retinitis	6,700	7,030	7,142

PUBLIC EDUCATION

Mr. Porter: What is the total budget for public education efforts for 1997?

Dr. Kupfer: The total budget for public education efforts for 1997 is \$1,067,000.

Questions Submitted by the Subcommittee

BLINDING EYE INFECTION

Mr. Stokes: We have been hearing a lot about the Institute's clinical trials including the EVS (endophthalmitis) trial and the CMV (cytomegalovirus) trial. What are the results thus far of the EVS trial, commonly known as the blinding eye infection disease trial? How widespread is this blinding eye infection, and what is the cost to society?

Dr. Kupfer: The EVS study has found that vitrectomy, a surgical procedure to replace the gel-like filling inside the eye, need not be performed on approximately 3/4 of patients who develop this bacterial infection that may occur after eye surgery. The trial also found that antibiotics given intravenously, for treating the same infection, provide no additional benefits over antibiotics given directly at the site of infection.

Although this infection occurs in only .4% of the 1.35 million people who have cataract surgery each year, the condition is considered very serious because it may lead to blindness.

The results of this clinical trial should mean fewer surgeries, and shorter or no hospital stays for as many as 5,400 people each year. This could result in health care cost savings of about \$40 million annually.

CLINICAL TRIALS

Mr. Stokes: What is the status of the Institute's CMV (cytomegalovirus) clinical trial?

Dr. Kupfer: There are 2 CMV clinical trials with recent findings. They are discussed below.

The CMV Retinitis Retreatment Trial has found that a daily intravenous administration of two antiviral drugs (foscarnet and ganciclovir) is a more effective way to treat repeat episodes of CMV retinitis than treatment with either drug alone. However, the two-drug therapy takes longer, because each drug has to be administered separately. In addition, the side effects associated with two-drug therapy may be more difficult to tolerate than those with one drug. Also, because two drugs are required, the treatment is more expensive than it would be if only one drug was used.

The second trial is the HPMPD Peripheral CMV Retinitis Trial. It has shown that a new drug, HPMPD, significantly slowed the progression of CMV retinitis, and was more convenient to administer than drugs now available. Because preliminary findings in the HPMPD Peripheral CMV Retinitis trial showed the drug to be effective, patient recruitment was stopped. Patients assigned to deferral of treatment who had not yet experienced disease progression were offered HPMPD. Follow up for all patients will continue for six months. HPMPD is now the subject of a New Drug Application to the U.S. Food and Drug Administration that requests marketing approval in the United States for treatment of CMV retinitis in people with AIDS.

Mr. Stokes: What other major clinical trials are underway at the Institute, and what is the expected benefit, in human health and economic savings from each?

Dr. Kupfer: Listed below are the other clinical trials underway at the NEI.

Advanced Glaucoma Intervention Study (AGIS)
 Central Vein Occlusion Study (CVOS)
 Collaborative Initial Glaucoma Treatment Study (CIGTS)
 Collaborative Ocular Melanoma Study (COMS)
 Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)
 Early Manifest Glaucoma Trial (EMGT)
 Effect of Light Reduction on Retinopathy (Light ROP)
 Herpetic Eye Disease Study - Phase II (HEDS II)
 Intravenous Immunoglobulin therapy in Optic Neuritis
 Ischemic Optic Neuropathy Decompression Trial (IONDT)
 Ocular Hypertension Treatment Study (OHTS)
 Optic Neuritis Treatment Trial (ONTT)
 Prospective Evaluation of Radial Keratotomy Study (PERK)
 Prospective Study of Diabetes Control and Retinopathy
 Quality of Life - The Collaborative Ocular Melanoma Study
 Randomized Trial for Retinitis Pigmentosa
 Randomized Trials of Vitamin Supplements and Eye Disease
 Short Wavelength Automated Perimetry in the OHTS Trial
 Studies of the Ocular Complications of AIDS (SOCA)
 Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity
 Age-Related Eye Disease Study (AREDS)

Listed below are examples of the human health and economic benefits derived from these clinical trials:

Diabetic Retinopathy - In addition to the enormous sight-saving benefits realized from NEI-sponsored research, this research has yielded significant cost savings over the last several years. For example, NEI-supported research has demonstrated that currently recommended treatments for diabetic retinopathy are over 95 percent effective in preventing blindness. It is estimated that these treatments save \$1.2 - 1.6 billion per year.

Cryotherapy for Retinopathy of Prematurity - This trial demonstrated the effectiveness of cryotherapy in halting the progression of the abnormal proliferation of blood vessels in the back of eyes of very premature infants. It is been estimated this treatment generates \$38 - \$65 million in savings each year.

Optic Neuritis Treatment Trial - This trial found that oral corticosteroids were not effective in treating optic neuritis, an acute debilitating inflammation of the optic nerve that primarily affects women. Investigators estimated that annual savings are approximately \$26 million in treatment costs.

Collaborative Corneal Transplantation Study - This study showed that donor-recipient tissue matching was not effective in reducing transplant rejection. Had the more costly HLA tissue typing become the standard practice, the cost of corneal transplantation would have risen by about \$1,000 per case.

Ischemic Optic Neuropathy Decompression Trial - This trial demonstrated that decompression surgery for ischemic optic neuropathy (the most common cause of sudden visual loss in older Americans) was no better than careful follow up and may even be harmful. It is estimated that \$30 - \$70 million will be saved annually by not performing this operation.

Mr. Stokes: How much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels of FY 1996, FY 1995, and FY 1994?

Dr. Kupfer: The funding levels for clinical trials, for FY 1994 - FY 1997, follow:

FY 1994	\$30,431,000
FY 1995	\$29,452,000
FY 1996	\$30,607,000
FY 1997	\$30,960,000

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: Where do we stand today with respect to closing the gap in minority health with respect to the diseases and disorders that are under the purview of your Institute? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Kupfer: The NEI, through the National Eye Health Education Program, launched its diabetic eye disease education program for Hispanics. The goal of this program is to increase awareness of the importance of a dilated eye examination at least once a year for the early detection and timely treatment of diabetic eye disease. Because many Hispanics receive their health information through television and radio, the initial phase of this program focused on working with the media. Public service announcements (PSAs) for television and radio and a video news release were released to the Spanish-language media and mainstream media in certain geographical locations with a high Hispanic population. In the current phase, the NEI is helping Hispanic community-based organizations to create a supportive environment for blindness prevention activities. Working through national and regional Hispanic organizations, the NEI staff are identifying programs that reach this target audience and providing technical assistance to these programs.

The NEHEP is working with the African American community to disseminate information on open-angle glaucoma. Open-angle glaucoma, the most common form of glaucoma, is a leading cause of blindness in the United States and the number one cause of blindness in African Americans. Although open-angle glaucoma can affect anyone, it is most prevalent in African Americans over age 40 and anyone over age 60. The NEHEP recommends that people at high risk have an eye examination through dilated pupils every two years. To reach high risk audiences, PSAs for television, radio, and the print media were developed. To help sustain the media activities, the NEI staff are working with community organizations, churches, worksites, and businesses to implement glaucoma education programs. The goal of these activities is to make glaucoma education a part of existing community health promotion and education programs. Technical assistance is given to other organizations to help them reach African Americans by identifying credible sources of information and strategies that are effective in empowering this community. Because African Americans are at high risk for diabetes, these same strategies are being implemented to reach African Americans with important information on diabetic eye disease.

To identify the most appropriate approaches to reach Native Americans, the NEI staff has conducted a preliminary review of the literature and interviews with experts working with Native Americans. This information will be used to plan a culturally sensitive education program. The NEI currently works closely with the Indian Health Service (IHS), the NEHEP Partnership, and other organizations to disseminate diabetic eye disease information to the Native American

community. New organizations and programs reaching Native Americans continue to be identified, as well as opportunities for future collaborations.

The NEI continues to monitor and revise its health education/communication strategies based on ongoing research and evaluation. This includes information obtained from "pilot programs" established by local communities in partnership with NEI staff, and preliminary data from the three related studies specifically targeted to at-risk populations for eye complications related to diabetes. The NEI plans to increase its efforts in monitoring community-based education programs and sharing the success and challenges of these programs with other interested parties. Through these various activities, the NEI will continue to be responsive to the blindness prevention needs of communities nationwide.

GENE REPOSITORY

Mr. Stokes: What is the association of genetic predisposition for the diseases and disorders under the purview of your Institute?

Dr. Kupfer: Molecular genetic techniques have opened up a new and exciting phase of research on a number of eye diseases. Hereditary eye diseases include retinitis pigmentosa, retinoblastoma, certain forms of macular degeneration, juvenile-onset glaucoma, aniridia, congenital stationary night blindness, familial exudative vitreoretinopathy, choroideremia, corneal dystrophies, and many others. Family history is a risk-factor for several complex eye diseases, such as open angle glaucoma and age-related macular degeneration.

Mr. Stokes: What can you tell us about the status of the gene repository as it relates to these diseases?

Dr. Kupfer: Genes have been mapped and/or isolated for most of the inherited eye diseases mentioned above. The number is quite large. Increasing attention is now focussed on understanding how these genes are regulated and how specific gene defects lead to pathophysiology. In many cases, animal models of human eye disease offer an additional promising avenue for research.

As might be expected, progress on complex eye diseases, such as open angle glaucoma and age related macular degeneration has been more difficult. It is likely that more than one gene is involved in these complex diseases, and environmental factors may be important. In the past year, the NEI was able to fund several outstanding new projects which are directed at finding the gene(s) involved in these complex eye diseases.

Mr. Stokes: What is the status of the gene repository as it relates to African Americans, and other minorities?

Dr. Kupfer: Glaucoma is a major public health problem and the number one cause of blindness in African Americans. A significant investment of resources has been directed toward elucidating the gene(s) involved in the most common form of glaucoma, adult onset, open angle glaucoma. The identification of "glaucoma" genes will open up a number of new clinical and research possibilities. One of the tragedies of this disease is that even though treatment exists, affected individuals are usually not diagnosed until irreversible nerve damage and, therefore, loss of vision has occurred. An immediate practical benefit of finding predisposing genes is that "at-risk" individuals could be identified and monitored so as to prevent vision loss.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in eye research?

Dr. Kupfer: The NEI remains very committed to and enthusiastic about the supplements program for underrepresented minority investigators. In FY 1995, NEI supported 41 minority individuals via this mechanism, 4 more than it did in FY 1994. Dollar support grew by 4.4 percent. Eighteen of the FY 1995 awards were for individuals new to the program. NEI extramural staff have made a number of presentations regarding this program and are working in close cooperation with several scientific and professional societies to publicize its availability.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: There is so much more we can and must do with respect to outreach and public education. The Institute's National Eye Health Education Program has brought critical attention to early diagnosis and treatment of sight threatening eye diseases and disorders including diabetic retinopathy and glaucoma. How much is included in the FY 97 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Kupfer: The funding levels for outreach and public education programs, for FY 1994 - FY 1997, follow.

FY 1994	\$1,323,000
FY 1995	\$1,000,000
FY 1996	\$1,050,000
FY 1997	\$1,067,000

Mr. Stokes: As these programs are funded in your research management and support account, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are we hurting the most?

Dr. Kupfer: Yes, these programs are funded in the NEI research management and support account. The NEI has been able to maintain its outreach and public education programs in spite of the funding reductions, by developing collaborative programs with organizations involved in the National Eye Health Education Program (NEHEP) Partnership. For example, the Lions Clubs International Foundation modeled its eye health program after the NEHEP by adapting existing NEHEP materials for use by Lions' members in their community.

RESEARCH MANAGEMENT AND SUPPORT

Mr. Stokes: The committee has been told that the NEI's research management and support account is not only very lean, but also extremely productive in terms of workload indicators. Can you provide us some specific examples of its productiveness?

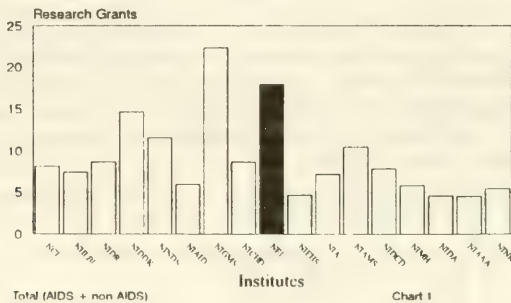
Dr. Kupfer: The NEI is considered one of the leanest NIH Institutes, and has some of the best workload ratios of the NIH Institutes. The three charts below illustrate this.

Charts 1 and 2 - Although the RMS staff includes a variety of position types that are necessary for an Institute to perform its mandated functions, a review of the number of grants per RMS FTE, as an indicator of staff activity, shows that NEI has the second highest number of grants among the Institutes during FY 1995. And looking at contracts and grants for the same period, reveals that NEI still had the second highest number of grants and contracts per RMS FTE among the Institutes.

Chart 3 - The "Report of the Committee to Review Full-Time Equivalents," (the Lenfant Report) published in November, 1992, contains data that further points to NEI's efficiency. The NEI has the largest ratio of extramural dollars to extramural program plus grant/contract management staff.

Research Grants/RMS FTE

FY 1995



Grants + Contracts per RMS FTE

FY 1995

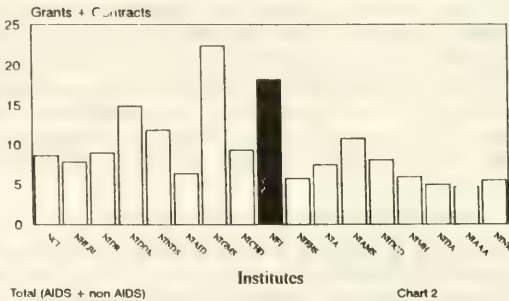
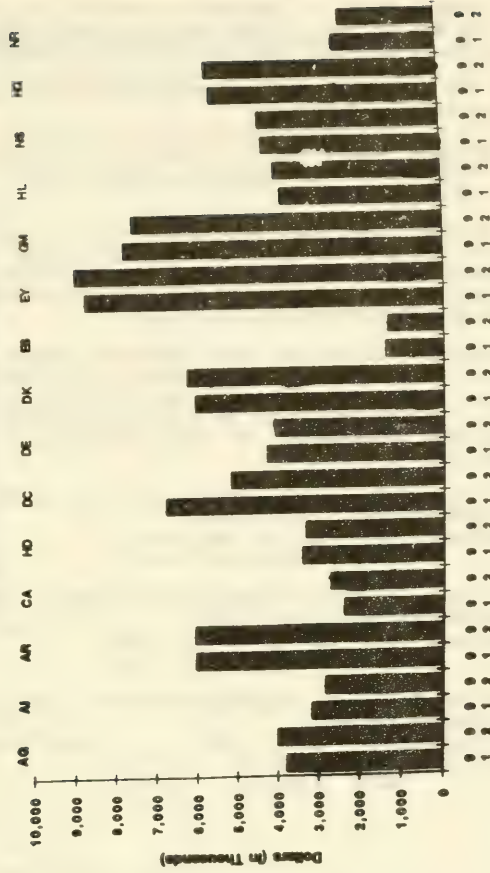


Chart 3
 Extramural Dollars Divided by Number of FTEs
 In Program Plus Grant/Contract Management Staff



OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway with your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the office, if so, which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Kupfer: In FY 1996, three such collaborative efforts are underway. None of these projects is funded totally by the Office of Research on Minority Health.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the office, if so what are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Kupfer: There are three specific projects which are administered by the NEI and which receive significant co-funding from the Office of Research on Minority Health (ORMH). These projects and the FY 1996 contributions from each organization are listed below. Future year ORMH commitments to these projects are negotiated on a year-to-year basis.

Project: Ocular Hypertension Treatment Study Center

Period of Performance: 1994 - 2003

FY 1996 Funding:	NEI	\$3,687,250	(81%)
	ORMH	\$850,000	(19%)

Project: Risk Factors for Diabetic Retinopathy in Blacks

Period of Performance: 1993 - 1997

FY 1996 Funding:	NEI	\$508,808	(71%)
	ORMH	\$210,000	(29%)

Project: Health Education Program for Diabetic Eye Disease in Oklahoma Indians

Period of Performance: 1992 - 1997

FY 1996 Funding:	NEI	\$355,455	(55%)
	ORMH	\$287,670	(45%)

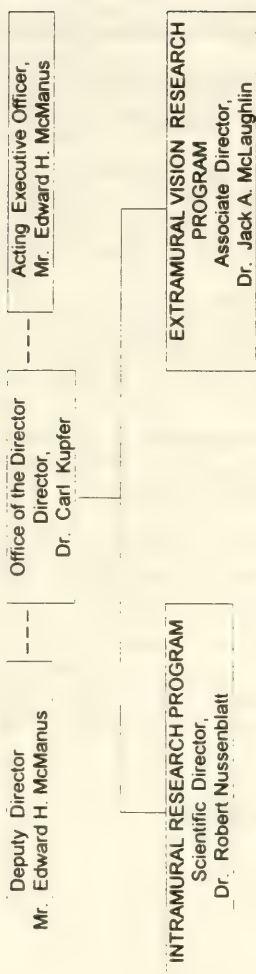
JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Eye Institute

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NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Eye Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to eye diseases and visual disorders, \$310,072,000.

Note — A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$291,600,000	\$314,185,000	\$310,072,000
Reduction in accordance with P.L. 103-333.....	-260,000		
Rescission in accordance with P.L. 104-19.....	-245,000		
Subtotal, adjusted Appropriation.....	291,095,000	314,185,000	310,072,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-248,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV Activities.....		-9,125,000	
Comparative transfer from: Other NIH Institutes for Management Fund adjustment..	+617,000		
Subtotal, adjusted budget authority.....	291,464,000	305,060,000	310,072,000
Unobligated balance, lapsing.....	-70,000		
Total obligations.....	291,394,000	305,060,000	310,072,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1995 -- \$10,406,000; 1996 -- \$12,000,000; 1997 -- \$12,000,000.

Also excludes funding for HIV activities: FY 1995 -- \$8,606,000; FY 1997 -- \$9,135,000, included in the Office of AIDS Research, NIH.

Justification

National Eye Institute

FY 1995		FY 1996		FY 1997		Increase or Decrease	
Actual		Estimate		Estimate			
FTE	BA	FTE	BA	FTE	BA	FTE	BA
241	\$291,464,000	235	\$305,060,000	235	\$310,072,000	0	+ \$5,012,000

This document provides justification for the FY 1997 Non-AIDS activities of the National Eye Institute. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

Out of concern for the thousands of Americans who were blinded each year by eye diseases and disorders of vision, Congress established the National Eye Institute (NEI) in 1968, giving it the broad responsibility to conduct and support research, training, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight and the special health problems of the blind. Subsequently, Congress added health education responsibilities to the mission of the NEI and appropriated funds to allow the Institute to increase its commitment to the prevention of blindness through public and professional education programs and the encouragement of regular eye examinations.

Diseases and disorders of the eye and visual system affect men and women, young and old alike, and cost our Nation an estimated \$22.3 billion in direct costs and \$16.1 billion in indirect costs each year. They have pronounced effects on quality of life, as indicated by the numerous surveys that have repeatedly demonstrated that Americans fear loss of vision more than any other disability.

Story of Discovery

Diabetic retinopathy is a sight-threatening complication of diabetes mellitus, in which the retinal blood vessels deteriorate and leak fluid into eye tissues. This fluid can collect in the macula, the part of the retina that provides sharp central vision, and cause macular edema, a swelling of the macula, and blurred vision. In some people, diabetic retinopathy progresses to a more advanced, proliferative stage in which abnormal blood vessels form on the surface of the retina. These fragile vessels can rupture and bleed into the eye or form scar tissue that contracts and causes retinal detachment.

Prior to the discovery of insulin in 1922, few people with insulin dependent (Type I) diabetes mellitus lived long enough to develop retinopathy, and therefore this complication was seen primarily in diabetics over the age of 40. Although the advent of insulin therapy improved the longevity of diabetics, it also resulted in an increase in the incidence and prevalence of diabetic retinopathy. In the early 1950s, the urgent need to develop an effective treatment that would prevent blindness led to the use of seemingly drastic procedures, such as pituitary ablation (destruction of the pituitary by surgery or radiotherapy). Despite significant complications associated with this procedure, it was effective to an extent in controlling the proliferation of blood vessels and subsequent loss of vision. By the end of that decade another procedure, photocoagulation (using a high intensity beam of light to coagulate proliferating and leaking retinal blood vessels), was also being examined for the treatment of diabetic retinopathy. Initially, the xenon arc was used as the light source, followed by the introduction of laser technology in the middle 1960s. During the 1960s, photocoagulation and pituitary ablation procedures continued to be employed and refined. In 1968, because of the alarming increase in blindness from diabetic retinopathy, the Public Health Service sponsored the Airlie House Symposium on the Treatment of Diabetic Retinopathy, which had as one of its goals determining the relative merits of the three primary treatments--tight control of blood glucose, pituitary ablation, and photocoagulation. Unfortunately, no consensus on the treatments could be achieved, and further studies were encouraged.

In 1971, the newly created National Eye Institute began the first in a series of prospective, randomized, collaborative, clinical trials, the Diabetic Retinopathy Study, to assist in resolving the controversy over the most effective treatment. This study demonstrated that visual disability arising from the proliferation of retinal vessels could be sharply reduced by extensive retinal photocoagulation with the xenon arc or argon laser. Subsequently, the Diabetic Retinopathy Vitrectomy Study demonstrated that the maintenance or recovery of vision can be improved when eyes with very severe proliferative diabetic retinopathy and/or hemorrhage undergo prompt vitrectomy (removal of the jelly-like vitreous in the middle of the eye). The Early Treatment Diabetic Retinopathy Study demonstrated that careful follow-up and deferral of scatter laser photocoagulation surgery until retinopathy approached the high-risk stage and focal laser treatment for diabetic macular edema were highly effective in preventing severe visual loss in nonproliferative or early proliferative disease. Today, currently recommended treatments arising from these studies are 90 percent effective in preventing blindness in patients with proliferative retinopathy. It is estimated that the treatment of diabetic retinopathy saves society \$1.2 - 1.6 billion per year. Research continues on the mechanisms involved in the development of diabetic retinopathy with the goal of discovering pharmacologic or other interventions that will prevent this blinding complication of diabetes from occurring.

Science Advances**Retinal Diseases**

The retina is a delicate, light-sensitive neural tissue at the back of the eye. Highly-specialized and metabolically active photoreceptor cells in the retina respond to light by emitting chemical and electrical signals. These signals are received by other retinal cells which process the signals and transmit visual information to the brain via the optic nerve. Diseases and disorders of the retina and the choroid, the underlying layer of blood vessels that nourish the retina, are the leading causes of blindness in the U.S. These sight-threatening conditions include age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, retinal detachment, and uveitis (ocular inflammation).

Molecular Basis of Signaling in the Retina The photoreceptor cells of the retina are very susceptible to damage from disease, hereditary defects, toxic agents, trauma, and dietary deficiencies. Once damaged, these cannot be replaced. A better understanding of the molecular machinery and cellular organization of the photoreceptor cells will help in the search for the causes of retinal diseases and for ways to prevent or treat these diseases. Scientists are in the process of establishing the complete molecular basis for the initiation, propagation, and termination of the visual signal, and for returning the photoreceptors to the dark-adapted state. Proteins, such as rhodopsin kinase and arrestin, have been shown to participate in the termination process. NEI-supported scientists have also discovered a novel calcium ion sensitive protein in the retina, guanylyl cyclase activating protein that may be a key participant in the recovery phase of the visual process.

Diabetic retinopathy Over time, diabetes can damage the blood vessels in the retina, resulting in impaired vision or blindness. Why do these changes occur and can they be prevented? Part of the answer to this question may lie in a better understanding of how cells of the retina cope with hypoxia (deficiency of oxygen) and how they respond to molecules called growth factors. Growth factors are relatively small protein molecules that stimulate the proliferation of cells. One of these growth factors, vascular endothelial growth factor (VEGF), may be very important in diabetic retinopathy.

Hypoxia in the retina is associated with diabetic retinopathy and appears to lead to formation of abnormal new blood vessels. Studies have demonstrated increased levels of VEGF in retinal cells cultured under hypoxic conditions. Recent research indicates that if a primate model is treated with a biological inhibitor (anti-VEGF monoclonal antibody) which blocks the function of VEGF, the development of new retinal blood vessels is suppressed. This is strong evidence that VEGF plays an important role in the formation of new blood vessels in the eye. The clinical relevance of these experiments appears high, as other studies have demonstrated dramatically elevated levels of VEGF within the eyes of patients with diabetic retinopathy. The results suggest that pharmacologic prevention of diabetic retinopathy may be possible.

Age-related macular degeneration. Macular degeneration is the generic name given to a number of eye diseases in which the central portion of the retina is destroyed. Age-related macular degeneration (AMD) is the most common cause of severe visual impairment in older persons in the U.S. Approximately 1.7 million Americans have decreased vision from AMD, and 100,000 are blind from the disease. The prevalence of decreased vision from AMD is expected to rise to 6.3 million by the year 2030, when an even greater percentage of our population will enter their retirement years. This disease robs otherwise healthy older Americans of their central vision, depriving them of the ability to read, drive, and to enjoy leisure activities that require good vision. There is no effective treatment for the vast majority of individuals with this condition.

The genes involved in the disease have been identified in at least two other types of macular degeneration, pattern dystrophy and Sorsby's dystrophy. In addition, the genes associated with several other forms of macular degeneration (progressive cone dystrophy, North Carolina macular dystrophy, Best's disease, cystoid macular dystrophy, and dominant radial drusen) have been localized to specific chromosomes. As scientists localize and then identify genes causing the various forms of macular degeneration, the study of the cellular and molecular basis of the disease will be facilitated. As the mechanism underlying each disease becomes better understood, improved therapies may be developed and administered before the onset of vision loss. A recent discovery by NEI-supported scientists supports this view.

Patients with Sorsby's fundus dystrophy experience night blindness, then central visual loss. In this disease, a genetic defect has been discovered in a protein that is thought to be involved in the maintenance of the subretinal extracellular matrix. Abnormal deposits become interposed between the photoreceptor cells of the retina and their blood supply, the choroid. Investigators hypothesized that these deposits may interfere with the transport of important nutrients, such as vitamin A, between the choroid and the photoreceptors. Vitamin A is well-known to be absolutely essential to vision and to the health and maintenance of the photoreceptors. In a dramatic test of this hypothesis, vitamin A supplementation was found to restore night vision in several patients with early-stage Sorsby's fundus dystrophy.

Molecular and Cell Biology of Retinitis Pigmentosa. Retinitis pigmentosa (RP) is a group of eye diseases in which the rod and cone photoreceptors in the retina degenerate. More than 100,000 Americans have RP. Individuals with RP typically report night blindness and loss of mid-peripheral vision during adolescence, and are usually legally blind by the age of 40.

Our understanding of RP has progressed rapidly with the discovery of many genetic mutations in photoreceptor genes. More than 15 genes have been implicated in different forms of RP through genetic linkage studies, and five genes have been identified. The identification of the genetic mutations in RP has allowed NEI-supported scientists to investigate the molecular mechanisms by which these mutant genes cause retinal dysfunction and photoreceptor degeneration. For example, a number of mutations in the rhodopsin gene and in the gene for the photoreceptor cGMP-gated channel are now known to lead to the production of misshaped proteins that are improperly transported within the cell and never reach the proper cell destination.

Neuron Survival Factor. Pigment epithelium-derived factor (PEDF) is a protein found in many cell types that has been known to induce a more differentiated character in human retinoblastoma tumor cells in culture. Recent work by NEI intramural scientists has shown PEDF to be a potent neuron-survival factor to a major neuronal cell type in the brain. Specifically, recombinant PEDF (rPEDF) added to cultures of cerebellar granule cells or CGCs (common neurons within the region of the brain known as the cerebellum) keeps the cells alive for long periods of time, i.e., much longer than their normal lifespan *in vitro*. Very low amounts of PEDF are needed for the survival effect. The effect is actually on cell survival, since PEDF does not stimulate cell proliferation of the CGCs. These results demonstrate that PEDF has a neurotrophic survival effect on the most abundant neuron in the cerebellum and suggests it may affect other central nervous system (CNS) neurons as well. The clinical potential is clear in that PEDF could be useful in treating any traumatic condition or inherited disease of the CNS where the survival of a neuron is threatened. Moreover, the potential use of PEDF in transplantation of CNS or other neural tissues to ameliorate diseases, such as Parkinson's Disease, retinal degeneration, etc., should be investigated.

Experimental Autoimmune Uveoretinitis. The ability to alter the immune response in an antigen-specific fashion has important implications for treatment of autoimmunity. The phenomenon of oral tolerance, or suppression of an immune response by feeding with the antigen, has been explored in a number of experimental models of autoimmune disease. The rat and mouse models of experimental autoimmune uveoretinitis (EAU) resemble some types of human uveitis, an ocular inflammatory process responsible for approximately 10 percent of the cases of legal blindness in the U.S. Earlier studies by NEI intramural researchers showed that EAU in rats can be suppressed by prior feeding with the eliciting uveitogenic antigen. Recent studies in mice have focused on using the EAU model to examine the feasibility of potentiating oral tolerance by immuno-manipulation. These studies suggested that enhanced suppression can be achieved by combining the feeding of antigen with administration of the cytokine IL-2, and possibly other cytokines, such as IL-4 or IL-10. It is hoped that this method will have practical application as a safe and effective way of potentiating oral tolerance in patients with uveitis based on the observation that the therapeutic window, as tested for the cytokine IL-2, is extremely broad, and the effective dose is well within the nontoxic range. The success of such a therapy would provide an alternative to the use of steroids in managing autoimmune ocular disease.

Gene Expression in the Retina. Investigators at the NEI have uncovered a number of new genes, some unique to the retina. Work on the specialized region of the retina called the macula has for the first time begun to demonstrate in a systematic way the complement of genes expressed in this area. Since the macula is responsible for color and sharp vision in primates, knowledge of gene expression in these region is critical to our understanding of the human visual process and in assembling a group of candidate genes that are responsible for hereditary and environmentally-induced macular degenerations.

Gene Therapy for Gyrate Atrophy. The use of gene manipulation as a therapeutic mode has become one of the most exciting areas of medicine. Intramural scientists at the NEI have launched studies to apply the methods of gene therapy to the treatment of genetic disorders

affecting vision. On the basis of work that has characterized the genetic defect and natural history of gyrate atrophy, an autosomal recessive disorder leading to blinding chorioretinal degeneration, scientists have conducted studies demonstrating that the insertion of a now-identified missing gene may have significant effect on the ocular disease. Additional studies aimed at using skin as a vehicle for inserting the missing gene are being tested. Current evidence suggests that the correction of this defect at a non-ocular location would lead to a marked amelioration or stabilization of this ocular disease with minimal risk to the patient.

Corneal Diseases

Diseases and injury to the cornea are the leading cause of visits to clinicians for eye care in the U.S. and rank among the most painful of eye conditions. NEI-supported research on corneal disease includes studies of ocular infections and inflammation, problems with tears and the ocular surface, refractive errors, corneal transplantation, and corneal wound healing.

Recurrent Ocular Infection by Herpes Simplex Virus-1. Herpes simplex virus (HSV-1) is a ubiquitous pathogen that causes skin lesions upon primary infection. The virus frequently establishes a latent infection in nearby sensory nerve cells, and can later be reactivated to cause recurrent disease in the skin and/or eyes. Ocular herpetic infections are painful, difficult to treat, and potentially blinding. NEI-supported researchers have been studying the molecular mechanisms of HSV-1 latency. One approach has been to study the promoter for the viral gene that codes for the only viral mRNA produced during latency. Interestingly, the activity of the viral LAT promoter varies enormously in different host neurons. Different host neurons thus produce different quantities or kinds of transcription factors that interact with the viral DNA in regulating the latent state. This work opens up promising new avenues for chemotherapy.

An alternate approach to the control of HSV-1 disease is the development of a vaccine. There has been a decided shift in research on ocular HSV-1 infections from studying viral antigens by conventional immunologic techniques to recombinant DNA studies of viral gene expression and structure. This approach has identified ten HSV-1 glycoproteins (gps) as the primary inducers and targets of immune responses to HSV-1 infection. NEI-supported researchers have produced gp vaccine "cocktails" and are screening various gp combinations to identify candidate vaccines.

Tear Formation. The seemingly simple process of water crossing the plasma membrane of a cell turns out to be a fundamental process, important in numerous physiological systems throughout the natural world. Surprisingly, the molecules that transport water remained unknown until three years ago, when the channel-forming integral protein or aquaporin (AQP) family was described. One member of this family, AQP5, has been implicated in secretion of the aqueous component of tears. The AQP5 gene has recently been cloned and NEI-supported studies are in progress to complete its sequence and chromosome localization. AQP5 has been hypothesized to play a role in Sjögren's Syndrome, an autoimmune condition associated with dry eye. Serum from patients suffering with Sjögren's Syndrome is being screened for reaction to AQP5 in order to assess the role of this transporter in pathogenesis.

Collaborative Longitudinal Evaluation of Keratoconus. Keratoconus is a visually disabling thinning disorder of the central cornea that results in irregular astigmatism, progressive corneal distortion, and corneal scarring. When severe scarring occurs, or when the visual distortion is beyond optical correction, the cornea is repaired or replaced by surgery.

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study is a NEI-supported multi-center, observational study designed to characterize the progression of keratoconus over a broad spectrum of disease severity. Information on participants's vision, quality of life, corneal shape, and corneal scarring is being collected to characterize the disease across its course and to identify risk factors and protective factors that determine the severity and progression of the disease. NEI-supported investigators are enrolling one thousand keratoconus patients at 15 participating U.S. clinical centers over the course of one year. Each patient is examined at baseline and annually for at least three years.

Lens and Cataract

Cataract is an opacity of the lens of the eye that interferes with vision. Cataract is a major public health problem. More than 1.5 million cataract surgical procedures are performed each year at a cost of more than \$5 billion. Reimbursements for this surgery account for approximately 12 percent of the entire Medicare Part B budget. The enormous economic burden of cataract will worsen significantly in coming decades as the American population ages. The NEI supports and conducts a number of research activities designed to determine the causes and mechanisms of cataract formation, to search for ways to slow or prevent the progression of cataract, and to develop and evaluate new diagnostic and therapeutic techniques in cataract management.

Molecular Genetics of Cataracts. For a number of cataracts, such as congenital cataracts, the underlying defects are secondary to metabolic or genetic diseases. Congenital cataracts account for 10 to 30 percent of all cases of blindness in children. This last year, considerable progress was made on one form of congenital cataracts--cataract associated with the disease galactosemia. The disease is caused by a deficiency in galactose kinase, an enzyme required for the metabolism of galactose, and is inherited in an autosomal recessive fashion (two copies of the defective gene are needed to cause the disease). Babies born with the disease develop cataracts within the first year of life.

The gene that encodes galactose kinase has recently been mapped to chromosome 17 and cloned. Three different forms of the gene have been identified: (1) the normal gene that encodes a properly functioning enzyme; (2) a gene with a single mutation that results in the wrong amino acid being placed in a critical site within the enzyme; and, (3) a gene in which a single mutation causes a shortened protein to be made. Babies that inherit two copies of the mutated forms of the gene are born with cataract. However, about 50 percent of the people who inherit one copy of the normal gene and one copy of one of the mutated genes go on to develop pre-mature (before the age of 50) cataract. With this new information, scientists can now develop animal models of this disease and gene therapy strategies can be investigated. Because galactosemia is characterized by an elevation in sugar galactose levels, the lens metabolism in these children is

similar to that seen in children with diabetes (elevation in glucose levels). A better understanding of the aberrant metabolism evident in this disease therefore, also has implications for the treatment of diabetic cataract.

Lens Cell Communication. Understanding the biology of the healthy lens is a necessary step in our search for ways to prevent cataract formation. The unique cellular structure of the lens requires a highly developed network of inter-cellular communication. The lens is a dense, compact structure containing two cell types: metabolically active epithelial cells and quiescent fiber cells. Unlike most other tissues, the lens is not nourished by its own blood supply and must take up nutrients from a circulating fluid called aqueous humor. Fiber cells are devoid of mitochondria and hence, are incapable of the energy-producing metabolism required for membrane transport. Fiber cells are dependent on the epithelial cells to extract nutrients from the aqueous humor. Nutrients are passed from epithelial cells to adjacent fiber cells and from fiber cells to more internal fiber cells. The channels that allow direct communication and passage of nutrients between cells are called gap junctions. An extensive network of epithelial-fiber cell and fiber-fiber cell gap junctions are needed to maintain the health of the lens and consequently, transparency.

The specialized proteins, connexins, that form gap junctions are being studied by a number of laboratories. Genes encoding lens-specific connexins have been cloned and expressed in a system that allows the connexins to be synthesized and assembled into functional gap junctions. Scientists are then able to investigate how two independent cells co-ordinate gap junction formation and how gap junctions function to mediate communication between cells. To date, genes that encode those connexins that form epithelial-epithelial cell and fiber-fiber cell gap junctions have been cloned and expressed, however, identifying epithelial-fiber cell gap junction proteins remains a challenge.

Endophthalmitis Vitrectomy Study. An NEI-supported clinical trial has found that vitrectomy, a surgical procedure to replace the gel-like filling inside the eye, need not be performed on approximately three-fourths of patients who develop a bacterial infection that may occur after eye surgery. The trial also found that antibiotic, given intravenously, for treating the same infection, provide no additional benefit over antibiotics given directly at the site of infection.

The infection, called endophthalmitis, causes an inflammation of the interior of the eye. Although occurring in only 0.4 percent of the estimated 1.5 million people who have cataract surgery each year, the condition is considered very serious because it may lead to blindness. The results of the clinical trial should mean fewer surgeries, and shorter or no hospital stays for as many as 5,400 people each year. This will result in potential savings of about \$40 million annually in health care costs. The clinical trial, called the Endophthalmitis Vitrectomy Study, involved 420 patients and was conducted at 27 university-based clinical centers and private practices nationwide.

Visualization of Biochemical Changes Associated with Sugar Cataract Formation. Nuclear Magnetic Resonance (NMR) and Magnetic Resonance Imaging are increasingly being used as research tools for studying various ocular diseases. Several of these techniques are currently

under development in NEI's intramural laboratories for the purpose of investigating biochemical changes associated with sugar cataract formation and quantitatively monitoring cataract formation in galactose-fed dogs. Magnetic resonance imaging, combined with magnetization transfer contrast (MTC) enhancement has been employed to improve visualization of cataractous tissue in galactosemic dog lenses. In addition to improved anatomical detail, this technique detects early tissue changes that are not detectable by optical means. Magnetic resonance imaging has documented changes in lens size and shape that have not been previously detected through optical means. To assess more fully these shape and volume changes, the MTC enhancement technique currently is being extended to the acquisition of 3-dimensional images. Magnetic resonance imaging is also being combined with NMR spectroscopy in order to measure noninvasively localized metabolic changes in the lens *in vivo*. A better understanding of the early structural and metabolic changes that occur in the lens prior to the development of a visible opacity or cataract may one day lead to the means to interrupt the pathologic process and slow or prevent the onset of cataract.

Molecular Genetics of Lens Crystallins. NEI intramural scientists have conducted studies that have defined the crystallins of both vertebrates and invertebrates at the gene level. These studies have made the lens a major model for molecular aspects of development and evolution. Recent work has delineated the mechanisms of crystallin gene expression in the lens and other tissues. With this knowledge, investigators have initiated genetic engineering in the visual system. These studies have led to many new insights on cellular and developmental aspects of the lens that lay the foundations for gene therapy in the lens.

Lens Opacification. Intramural investigators are also inducing opacification of lenses in organ culture to study the effect of specific chemical agents or combinations of such agents on preventing cataractous lens changes. The general hypothesis is that while cataracts are multifactorial in etiology and may be initiated by a wide variety of insults, there are probably a limited number of common pathways involved in the progression of the opacification process. Therefore, the best approach to preventing or delaying cataract development is through targeting these putative common pathways which are part of the cascade of events that follow the initiating insult(s). Previous studies demonstrate that these pathways may involve oxidation, proteolysis, phase separation, glycation, etc. A large number of compounds have been tested individually and in various combinations using the lens organ culture system. Certain compounds with putative oxidative properties have been found to effectively prevent lens opacification in the culture system. Additional studies are now underway to determine whether these specific agents can be utilized in animals to prevent or inhibit cataract formation.

Glaucoma

Glaucoma is a group of eye disorders which share a distinct type of optic nerve damage which can lead to blindness. Elevated intraocular pressure is frequently, but not always, associated with glaucoma. Glaucoma is a major public health problem and the number one cause of blindness in African Americans. Approximately 3 million Americans have glaucoma, and as many as 120,000

are now blind from this disease. Blindness from glaucoma is estimated to cost the U.S. in excess of \$1.5 billion annually in Social Security benefits, lost tax revenues, and health care expenditures. The NEI is supporting a number of studies directed toward understanding the mechanisms of the disease through basic research, identifying risk factors, and preventing blindness.

Diagnostic instruments. Several new instruments are being developed to measure changes in optic nerve structure and function in glaucoma. Glaucoma is characterized by a distinct type of damage to nerve fibers as they travel from the ganglion cell layer of the retina through the optic nerve head to make their connections in the brain. Two new diagnostic instruments that are currently being tested in longitudinal studies are optical coherence tomography (OCT) and confocal scanning laser polarimetry (CSLP). As glaucomatous damage takes place, the retinal nerve fiber layer (RNFL) thins due to loss of nerve fibers. Using these instruments, RNFL thinning in an individual glaucoma patient can be followed over time to chart the progression of the disease. Both instruments measure the same thing but do so by taking advantage of different properties of light, OCT uses infrared light whereas the CSLP uses a laser beam. Longitudinal studies are underway to determine the clinical usefulness of each of these instruments.

Automated perimetry is routinely used to assess the visual loss that is produced by glaucoma. Recent modifications of this device have improved its predictive power. Short-wavelength perimetry or SWAP capitalizes on reduced perception of color in glaucoma patients by measuring an individual's ability to detect blue light flashed on a yellow background. A five year longitudinal study is underway. The test is proving invaluable for ocular hypertensives, those individuals with high intraocular pressure but no signs of glaucoma. Only about 1-2 percent of these patients per year will eventually go on to develop glaucoma, and it is not currently possible to predict those who are at risk from those who are not. The new SWAP test may be superior to perimetric tests now in routine use. In ocular hypertensives, SWAP may detect vision loss 3-5 years earlier and appears to be a better indicator of who is at immediate risk for developing glaucoma.

Molecular Genetics of Glaucoma. Some forms of primary open angle glaucoma (POAG), for instance the juvenile form, are clearly inherited. However, these forms are relatively rare. Studies on adult-onset POAG, the most predominant form, indicate a genetic component. For example, the chances that a sibling of a glaucoma patient will get glaucoma is thought to be at least 7-10 times greater than a person with no known glaucoma in his/her family. In adult-onset POAG, the genetic component likely confers a predisposition or increased susceptibility to the disease.

In an attempt to better characterize adult-onset POAG, a number of research initiatives are underway to identify underlying genetic factors. A gene for the juvenile form of POAG has been identified on an 8-9 centimorgan region of chromosome 1. Although it is widely believed that this form of the disease is distinct from the adult-onset POAG, it is hoped that further work in this area may suggest possible candidate genes for adult POAG.

The identification of "glaucoma" genes will open up a number of new clinical and research possibilities. One of the tragedies of this disease is that even though treatment exists, affected individuals are usually not diagnosed until irreversible nerve damage and, therefore, loss of vision

has occurred. An immediate practical benefit of finding predisposing genes is that "at-risk" individuals could be identified and monitored so as to prevent vision loss.

Laser Surgery. Findings from the recently completed Glaucoma Laser Trial Follow-up Study (GLTFS) indicate that laser surgery is a safe and effective alternative to eyedrops as a first-line treatment for patients with newly diagnosed primary open-angle glaucoma. The GLTFS was done to learn if early laser treatment is safe and whether it offers any medical advantages over eyedrops for patients with newly diagnosed open-angle glaucoma. The trial was conducted among 271 patients with 203 patients completing seven years of followup. Each patient had laser treatment in one eye and medication in the other eye. After some 7 years of followup, the "laser first" eyes and the "medication first" eyes had a similar status on all measures used to evaluate the two treatments.

Strabismus, Amblyopia, and Visual Processing

Developmental disorders such as strabismus, misalignment of the eyes, and amblyopia, commonly known as "lazy eye", affect 2-4 percent of the U.S. population. The correction of strabismus is one of the most frequently performed of all surgical procedures. In addition to research relevant to strabismus and amblyopia, the NEI supports investigations of the age-related inability of the lens to focus on nearby objects, irregular eye movements, and refractive errors. Three million Americans now have chronic visual conditions that are not correctable by eye glasses or contact lenses. Therefore, the NEI also supports research on improving the quality of life of persons with visual impairments by helping them maximize the use of remaining vision and by devising aids to assist those without useful vision.

Development of Myopia and Related Refractive Errors. More than 25 percent of the adult population of the United States is nearsighted (myopic). Recent experimental findings have provided significant insights into the development of myopia and may lead to preventive strategies that can be tested through appropriate clinical trials.

Although human infants don't usually see very well, during the first two to three years of life, the eyes of most individuals develop to nearly ideal optical states. How does this occur, and what goes wrong in individuals who become nearsighted? One goal of NEI-supported research is to test the hypothesis that eye development is regulated by visual feedback. A recent study used spectacle lenses to simulate nearsightedness (myopia), or farsightedness in one eye of infant monkeys and measured the effect on the eye's growth. Lenses that artificially made an eye farsighted caused the eye to grow longer than normal in order to compensate. Alternatively, lenses that simulated nearsightedness led to a reduction in ocular growth.

This research prompted experiments to determine what causes the eye to grow longer or shorter in response to whether the visual image is blurred or not. Recent studies have shown that the structural nature of the outer coat of the eye, the sclera, changes when the visual input is blurred. These structural changes in the sclera may make the eye less resistant to the internal pressure, causing the eye to elongate.

Guidance of Visual Nerve Processes During Development. The visual information that is received by our eyes is projected in a very precise manner to the visual centers of the brain where this information is integrated into a coherent perception of the world. A question of fundamental importance is how nerve processes which exit the retina of the eye are guided during embryonic development to form precisely mapped connections within the brain. At the X-shaped optic chiasm at the base of the brain, nerve processes coming from the retinas of both eyes must "choose" to grow either to the right or to the left side of the brain. This choice is critical to proper visual function.

Recently, a distinct group of nerve cells has been located in the optic chiasm that appears to act as a signpost, guiding the ingrowing retinal processes to the proper pathway. When the chiasm neurons are removed, retinal processes grew up to the chiasm, but were unable to grow further and did not form connections in the brain. Future work should tell us more about such developmental guidance mechanisms, and whether these mechanisms can be manipulated to promote regeneration of the visual system after injury or disease.

Factors Controlling Nerve Cell Growth. For years, most researchers thought nerve cells in the brain and the spinal cord could not regenerate after disease or injury. Then came the discovery that factors in the microenvironment of the central nervous system could stimulate or inhibit the growth of nerve cell processes. This discovery encouraged researchers to think that, given the right conditions, severed nerve cell processes could re-establish their connections. Until recently, no one has been able to get these processes to regrow in large numbers. Investigators placed retinal cells from animals in a laboratory dish next to tissue from the midbrain tectum, a target area that retinal axons normally innervate during development. They found that almost all retinal axons in culture would connect with tectal cells up to ages two to four days postnatally, but very few retinal axons from older animals would make connections when cultured in the same way. This is support for the hypothesis that the genes in nerve cells that control elongation of processes "turn off" at a certain point in development. This new experimental system should help investigators determine how neuronal genes and factors in the microenvironment interact to control the development of appropriate connections within the visual system.

Control of Eye Movement. Scientists in the NEI's intramural laboratories are conducting studies on the control of movement by visual input and the systems in the brain that carry out this vital function. One of the most fundamental problems that the brain must solve is to keep track of the movements being generated. Recently, scientists found that the activity of a type of neuron in the superior colliculus seems to keep track of the generation of saccadic eye movements by integrating the spread of activity among the cells. One test of this hypothesis has used the disruption of these cells by minute injection of drugs; the results have been consistent with the hypothesis. Another approach has been to use neural models to see if the principles could control simulated eye movements; they can. This increased understanding of the visual-oculomotor system not only should contribute to diagnosis of the disorders of eye movement but also to the search for simpler mechanisms in other movement control systems.

Benefits and Impact of Research

In addition to the enormous sight-saving benefits realized from NEI-sponsored research, this research has yielded significant savings over the last several years. For example, NEI-supported research has demonstrated that currently recommended treatments for diabetic retinopathy are over 95 percent effective in preventing blindness. It has been estimated that these treatments save \$1.2 - 1.6 billion per year. The Cryotherapy for Retinopathy of Prematurity Study demonstrated the effectiveness of cryotherapy in halting the progression of the abnormal proliferation of blood vessels in the back of eyes of very premature infants. It is estimated this treatment generates \$38 - \$65 million in savings each year. The Optic Neuritis Treatment Trial found that oral corticosteroids were not effective in treating optic neuritis, an acute debilitating inflammation of the optic nerve that primarily affects women. Scientists estimated that the annual savings could be approximately \$26 million in treatment costs. The Collaborative Corneal Transplantation Study showed that donor-recipient tissue matching was not effective in reducing transplant rejection. Had the more costly HLA tissue typing become the standard practice, the cost of corneal transplantation would have risen by about \$1,000 per case. The Ischemic Optic Neuropathy Decompression Trial demonstrated that decompression surgery for ischemic optic neuropathy (the most common cause of sudden visual loss in older Americans) was no better than careful follow up and may even be harmful. It is estimated that \$30 - \$70 million will be saved annually by not performing this operation.

In an attempt to determine whether there are any measures of the impact of NEI-supported research on commercial activities, the NEI has assessed the linkage between supported research and U.S. patent activity. The support for vision research has provided an important foundation for the development of drugs, devices, and biotechnologies. In fact, 40 percent of all research papers referenced as prior art by more than 8,000 eye-related U.S. patents issued since 1975, acknowledged either NEI or other NIH support. This diverse patent portfolio covers everything from eyeglasses and intraocular lenses to medicines and high technology surgical instruments.

In order to better evaluate the impact of NEI research on the patient's quality of life, the NEI is supporting the development and evaluation of an instrument (questionnaire) to assess visual functioning and its effect on health-related quality of life, as self-reported by the patient. This instrument, the NEI Visual Function Questionnaire (NEI-VFQ), will be a useful complement to traditional clinical measures of vision, not only for use in clinical trials as an outcome measure, but also in medical practice.

Patients undergoing treatment for eye or vision related problems often are faced with options that relate more to improving the quality rather than the length of life. Nonetheless, the potential benefits and risks associated with the treatment must be carefully weighed by the patient and health care providers in terms of effectiveness and potential outcome. Recognizing the need for a means to assess the effects of treatment on how patients feel about the potential outcomes, the NEI is also undertaking a pilot study using utility assessment to formally quantify patient preferences for potential health state outcomes. These utilities are designed to capture the degree

to which patients are bothered by a particular outcome. They typically range from 0 to 1, with 1 representing the best possible outcome, and 0 representing the worst possible outcome (often death). They also allow comparisons of outcomes across disease conditions, including comparisons of life-threatening conditions with non life-threatening morbidity, such as comparing the risk of shortened life expectancy with the risk of blindness. This type of utility assessment not only provides a means for the patient and providers to evaluate the benefit of treatment, it also may be useful in the allocation of medical service resources across diseases and conditions.

Budget Policy

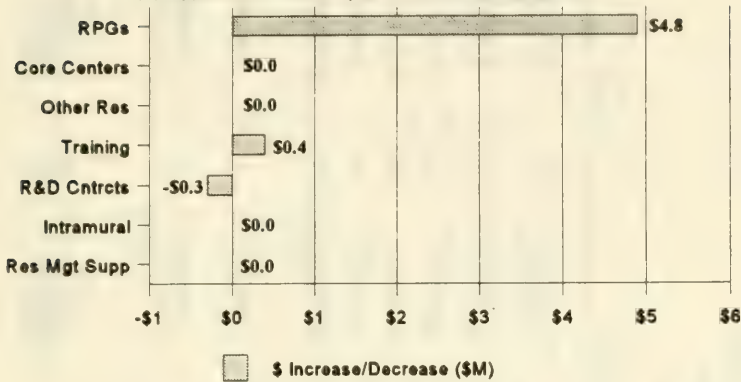
The NEI is requesting a total of \$310.1M, an increase of 1.6 percent or \$5M over the FY 1996 level. Within the \$5M increase, \$2M is earmarked for the Special Emphasis Area "Biology of Brain Disorders" and will be used for new and competing research project grants in the area of visual neuroscience. Other research opportunities to be pursued at the FY 1997 level, include molecular genetics of glaucoma, retinal degeneration, and cataract; and biochemical factors related to the development of diabetic retinopathy.

NIH plans to revise average cost increases in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 249 competing RPGs, an increase of 26 competing RPGs over FY 1996, and 976 total RPGs, the same level of RPGs as in FY 1996.

Within the overall \$5M increase, NEI support for research project grants (RPGs) would increase by 1.8 percent over FY 1996. NEI support for training awards are proposed to receive an increase of \$.4M, as a result of a proposed increase in stipend levels. Also, R&D contracts are proposed to receive a 3 percent funding reduction or \$.3M, and funding for intramural research and research management and support are proposed to remain at the FY 1996 level.

NATIONAL EYE INSTITUTE

FY 1996 VS. FY 1997 - \$ CHANGE BY MECHANISM



NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Mechanism

	1995 Actual	No.	Amount	1996 Estimate		1997 Estimate	
				No.	Amount	No.	Amount
Research Grants:							
Research projects							
Noncompelling	715		\$147,378,000	713	\$149,598,000	679	\$146,261,000
Admin. Supplemental	(49)		1,551,000	(30)	2,071,000	(30)	2,112,000
Compelling							
Renewals	134		31,459,000	133	32,407,000	148	36,955,000
New	91		15,653,000	90	16,070,000	101	18,486,000
Supplemental							
Subtotal, competing	225		47,112,000	223	48,477,000	249	55,441,000
Subtotal, research projects	940		196,041,000	936	200,146,000	928	203,814,000
SBIR/STTR	38		5,417,000	40	5,727,000	48	6,932,000
Total, research projects	978		201,458,000	976	205,873,000	976	210,746,000
Research Centers							
Core/specialized	30		8,340,000	31	8,954,000	31	8,954,000
Other Research:							
Research Career prog	20		1,651,000	25	2,500,000	30	3,000,000
Cooperative clin. res	134		22,666,000	188	29,441,000	188	28,941,000
Biomedical research support							
Minority biomedical support			299,000				
Other res. related	4		789,000	13	375,000	13	375,000
Subtotal, other res.	158		25,385,000	226	32,780,000	231	32,780,000
Total, research grants	1,166		235,183,000	1,233	247,607,000	1,238	252,480,000

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Training:						
Individual awards						
Noncompeting.....	60	\$1,722,000	49	\$1,517,000	49	\$1,596,000
Competing.....	56	1,461,000	46	1,295,000	46	1,364,000
Subtotal, individual awards.....	116	3,183,000	95	2,812,000	95	2,960,000
Institutional awards						
Noncompeting.....	134	3,336,000	132	3,778,000	132	3,976,000
Competing.....	43	979,000	43	1,125,000	43	1,185,000
Subtotal, institutional awards.....	177	4,315,000	175	4,903,000	175	5,161,000
Total training.....	293	7,498,000	270	7,715,000	270	8,121,000
Research & development contracts.....	19	8,270,000	26	8,859,000	26	8,592,000
	FTEs		FTEs		FTEs	
Intramural research.....	174	29,443,000	167	30,467,000	167	30,467,000
Research management and support.....	67	11,070,000	68	10,412,000	68	10,412,000
TOTAL.....	241	291,464,000	235	305,060,000	235	310,072,000
Clinical Trials		(25,030,000)		(26,254,000)		(26,661,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
EXTRAMURAL RESEARCH												
Vision Research	202	\$229,891	186	\$242,277	174	\$250,951	167	\$264,181	167	\$269,193	0	+\$5,012
Intramural Research	70	11,207	67	10,892	67	11,070	68	10,412	68	10,412	0	0
Research management and support	272	269,085	253	282,106	241	291,394	235	305,060	235	310,072	0	+\$5,012
Total obligations												
Unobligated balance lapsing		+549		+354		+70						
Total, budget authority	272	269,634	253	282,460	241	291,464	235	305,060	235	310,072	0	+\$5,012

Note Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Summary of Changes

1996	Estimated budget authority.....	\$305,060,000
1997	Estimated budget authority.....	310,072,000
	Net change.....	+5,012,000

		1996 Current		Change from Base	
		Estimated Base		Budget	
		FTE	Authority	FTE	Authority
Changes					
A.	Built-in:				
1.	Intramural:				
a.	Within grade increase	\$13,131,000			+\$197,000
b.	One less day of pay.....	13,131,000			--
c.	Annualization of January				
	1996 locality pay.....	13,131,000			+85,000
d.	FY 1997 pay increases	13,131,000			+302,000
e.	FECF Unemp. Comp.....	13,131,000			+3,000
f.	Payment for Mgmt				
	fund.....	7,702,000			+\$1,068,000
g.	Service and supply fund				
	increase.....	9,634,000			+212,000
	Subtotal.....				+1,867,000
2.	Research Management & Support:				
a.	Within grade increase	4,300,000			+65,000
b.	One less day of pay.....	4,300,000			--
c.	Annualization of January				
	1996 locality pay.....	4,300,000			+28,000
d.	FY 1997 pay increase	4,300,000			+99,000
e.	FECF Unemp. Comp.....	4,300,000			--
f.	Payment for Mgmt				
	fund.....	2,504,000			-130,000
g.	Service and supply fund				
	increase.....	3,608,000			+79,000
h.	DHHS Working Capital				
	Fund decrease	0			--
i.	FTS decrease.....	500,000			--
	Subtotal.....				+141,000

B. Program		No.	Amount	No.	Amount
1.	Research project grants:				
a.	Noncompeting.....	713	151,669,000	-34	-3,296,000
b.	Competing.....	223	48,477,000	+26	+6,964,000
c.	SBIR/STTR.....	40	5,727,000	+8	+1,205,000
	Total.....	976	205,873,000	0	+4,873,000
2.	Center grants.....	31	8,954,000	---	---
3.	Other research.....	226	32,780,000	+5	---
4.	Training.....	270	7,715,000	---	+406,000
5.	Research and development contracts.....	26	8,859,000	---	-267,000
6.	Intramural research.....	<u>FTE</u> 161	30,467,000	<u>FTE</u> ---	-1,867,000
7.	Research management and support.....	66	10,412,000	---	-141,000
	Subtotal.....				+3,004,000
	Total changes.....				+5,012,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable workyears: Full-time equivalent employment.....	235	235	—
Full-time equivalent of overtime and holiday hours.....	—	—	—
Average ES salary.....	\$118,000	\$121,000	+\$3,000
Average GM/GS grade.....	10.6	10.6	—
Average GM/GS salary.....	\$50,000	\$51,000	+\$1,000
Average salary, grade established by act of July 1, 1944 (42 U.S. C. 207).....	\$60,000	\$62,000	+\$2,000
Average salary of ungraded positions.....	N.A.	N.A.	—
Personnel compensation:			
Permanent positions.....	\$9,233,000	\$9,510,000	+277,000
Positions other than permanent.....	3,110,000	3,203,000	+93,000
Other personnel compensation.....	387,000	399,000	+12,000
Special personnel services.....	<u>1,970,000</u>	<u>2,084,000</u>	<u>+114,000</u>
Total personnel compensation.....	14,700,000	15,196,000	+496,000

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Personnel benefits.....	2,860,000	2,906,000	+246,000
Benefits for former personnel.....	10,000	11,000	+1,000
Travel and transportation of persons.....	467,000	467,000	—
Transportation of things.....	57,000	57,000	—
Communications, and miscellaneous charges.....	500,000	500,000	—
Printing and reproduction.....	211,000	211,000	—
Other Services:			
Consultant services.....	188,000	188,000	—
Other Services.....	1,342,000	1,343,000	+1,000
Purchases from Govt. cts.....	15,862,000	15,116,000	-746,000
Operation of GOCOs.....	390,000	390,000	—
R&D Contracts.....	8,859,000	8,592,000	-267,000
Supplies and materials.....	2,704,000	2,704,000	—
Equipment.....	1,727,000	1,727,000	—
Grants, subsidies and contributions.....	255,322,000	260,601,000	+5,279,000
Insurance Claims and Indemnities.....	<u>61,000</u>	<u>63,000</u>	<u>+2,000</u>
Total, budget authority by object.....	305,060,000	310,072,000	+5,012,000

Note: Includes 8 FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Administrative Costs

	1996 Estimate	1997 Estimate	Increase or Decrease
Personnel Compensation:			
Full-time Permanent (11.1).....	\$9,233,000	\$9,510,000	+\$277,000
Other than Full-Time Permanent (11.3).....	3,110,000	3,203,000	+93,000
Other Personnel Compensation (11.5).....	387,000	396,000	+12,000
Special Personnel Services (11.8).....	<u>1,970,000</u>	<u>2,084,000</u>	<u>+114,000</u>
Total Personnel Compensation (11.9).....	14,700,000	15,196,000	+496,000
Civilian Personnel Benefits (12.1).....	2,660,000	2,906,000	+246,000
Benefits for Former Personnel (13.0).....	10,000	11,000	+1,000
Travel (21.0).....	467,000	467,000	—
Transportation of things (22.0).....	57,000	57,000	—
Communications, utilities, and miscellaneous charges (23.3).....	500,000	500,000	—
Printing and reproduction (24.0).....	211,000	211,000	—
Consultant Services (25.1).....	188,000	188,000	—
Other Services (25.2).....	1,342,000	1,343,000	+1,000
Purchase of goods and services from Government Accounts (25.3).....	13,974,000	13,286,000	-688,000
Operation & Maintenance of Facilities (25.4).....	390,000	390,000	—
Operation & Maintenance of Equipment (25.7).....	581,000	581,000	—
Supplies and materials (26.0).....	<u>2,704,000</u>	<u>2,704,000</u>	<u>—</u>
Total.....	37,784,000	37,840,000	+56,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Investigator-Initiated Research Grants - . . . The House in its report 104-209, page 70, stated "The Committee also acknowledges the strategy of NEI to emphasize the investigator-initiated research grant. Turnover within this research portfolio frees funds for new grants even in times of restricted budgets. The Institute is encouraged to maintain this policy to the extent it believes it continues to be appropriate."

Action Taken or to be Taken

The NEI plans to continue making awards for basic research in such a way as to maximize opportunities for individual investigators. To this end, the NEI does not award program project grants or other types of "umbrella" mechanism of research support, issue Requests for Applications for basic research projects, or fund clinical trials using research project grants. As a result, the entire NEI research project grant category supports individual investigator-initiated research. These management decisions have the effect of increasing the NEI success rate relative to that of the other Institutes

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

National Eye Health Education Program (NEHEP) - . . . The House in its report 104-209, page 70, stated "NEI has developed a comprehensive eye health program in diabetic retinopathy and glaucoma. The Committee is pleased that this program is being adapted to the specific needs of the Hispanic/Latino community, where diabetic retinopathy is especially prevalent. The committee encourages NEI to evaluate and redefine its communication strategies as new information emerges from ongoing research."

Action Taken or to be Taken

The NEI, through the National Eye Health Education Program, launched its diabetic eye disease education program for Hispanics. The initial phase of this program focused on working with the media to increase awareness of the importance of early detection and timely treatment of diabetic eye disease. The NEI also is working with Hispanic community-based organizations to create a supportive environment for blindness prevention activities. The NEI continues to monitor and revise its health education/communication strategies based on ongoing research and evaluation. This includes information obtained from "pilot programs" established by local communities in partnership with NEI staff, and preliminary data from the three related studies specifically targeted to at-risk populations for complications of diabetic eye disease. The NEI plans to increase its effort in monitoring community-based education programs and sharing the success and challenges of these programs with other interested parties. Through these various activities, the NEI will continue to be responsive to the blindness prevention needs of communities nationwide.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Authorizing Legislation

	PHS Act/Other Citation	U S Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Budget Request
Research and Investigation	Section 301	42§241	Indefinite	\$296,201,000	Indefinite	\$301,480,000
National Eye Institute	Section 455	42§851	Indefinite		Indefinite	
Service Awards	Section 487 (d)	42§288	Such sums as necessary	\$8,859,000	Authorization pending	\$8,592,000
Total, Budget Authority				\$305,060,000		\$310,072,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987 2/	\$179,201,000	\$219,091,000	\$214,080,000	\$216,637,000
1988	184,829,000	234,382,000 3/	231,529,000	224,947,000
1989	229,021,000 4/	223,288,000 5/	229,271,000	234,218,000
1990	223,777,000 6/	240,636,000	241,774,000	239,889,000 7/
1990 Sequester				-3,356,000
1991	247,392,000	254,887,000 8/	258,324,000	253,241,000 9/
1991 Sequester				-3,000
1992	272,260,000	272,260,000	267,229,000	269,300,000 10/
1993	285,133,000	279,102,000	279,102,000	276,188,000 11/
1994	272,201,000	290,260,000	290,260,000	290,260,000
1995 12/	292,022,000	290,199,000	291,886,000	291,340,000 13/
1995 Rescission				-245,000
1996	300,693,000 12/	314,185,000	297,489,000 12/	314,185,000
1997 12/	310,072,000			

- 1/ Reflects enacted supplementals, rescissions, and reappropriations
 2/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH. The Senate Allowance and the appropriation spread the funding among the Institutes, including \$104,000 for the NEI.
 3/ Does not include funding for AIDS research consolidated at the Secretary's level.
 4/ The 1989 request excludes funds for AIDS research and education (\$4,947,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
 5/ Excludes \$5,620,000 in NRSA training programs not considered.
 6/ The 1990 request excludes funds for AIDS research and education (\$5,697,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
 7/ Excludes enacted administrative reductions of \$1,316,000.
 8/ Excludes \$7,105,000 in NRSA training programs not considered.
 9/ Excludes enacted administrative reductions of \$6,918,000.
 10/ Reflects enacted administrative reductions of \$1,702,000.
 11/ Reflects enacted administrative reductions of \$2,914,000.
 12/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
 13/ Excludes enacted administrative reductions of \$138,000, \$7,000, and \$115,000.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of Full-Time Equivalent Employment (FTE)

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Office of the Director.....	40	40	40
Intramural Research Program	174	167	167
Extramural Vision Research.....	<u>27</u>	<u>28</u>	<u>28</u>
Total, NEI.....	241	235	235

Average GS/GM Grade

1992	10.5
1993	10.5
1994	10.6
1995	10.6
1996	10.6
1997	10.6

Note: Includes 8 FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General.....			
Director Grade.....	3	3	3
Senior Grade.....	3	3	3
Full Grade.....	2	2	2
Senior Assistant Grade.....			
Assistant Grade.....			
Subtotal.....	8	8	8
Ungraded.....	53	48	48
Total permanent positions.....	245	240	240
Total positions, end of year.....	245	240	240
Total full time equivalent (FTE) employment, end of year.....	241	235	235
Average ES level.....	4.7	4.7	4.7
Average ES salary.....	109,800	111,800	113,600
Average GS/GM grade.....	10.6	10.6	10.6
Average GS/GM salary.....	47,000	48,000	49,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
Executive level I.....			
Executive level II.....			
Executive level III.....			
Executive level IV.....			
Executive level V.....			
Subtotal.....	0	0	0
Total - Exec. Lev.			
Sal.....			
ES-6.....	1	1	1
ES-5.....	2	2	2
ES-4.....	3	3	3
ES-3.....			
ES-2.....			
ES-1.....			
Subtotal.....	6	6	6
Total - ES Salary.....	\$658,700	\$670,900	\$681,800
GS/GM-15.....	21	21	21
GS/GM-14.....	24	24	24
GS/GM-13.....	12	12	12
GS-12.....	25	25	25
GS-11.....	32	32	32
GS-10.....	2	2	2
GS-9.....	11	11	11
GS-8.....	13	13	13
GS-7.....	16	16	16
GS-6.....	7	7	7
GS-5.....	4	4	4
GS-4.....	8	8	8
GS-3.....	2	2	2
GS-2.....	1	1	1
GS-1.....	0	0	0
Subtotal.....	178	178	178

MONDAY, APRIL 22, 1996.

**NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES
AND STROKE; NATIONAL INSTITUTE OF MENTAL
HEALTH; NATIONAL INSTITUTE ON DRUG ABUSE; NA-
TIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCO-
HOLISM**

WITNESSES

**DR. ZACH W. HALL, DIRECTOR, NATIONAL INSTITUTE OF NEURO-
LOGICAL DISORDERS AND STROKE**

**DR. STEPHEN E. HYMAN, DIRECTOR, NATIONAL INSTITUTE OF MEN-
TAL HEALTH**

**DR. ALAN I. LESHNER, DIRECTOR, NATIONAL INSTITUTE ON DRUG
ABUSE**

**DR. ENOCH GORDIS, DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL
ABUSE AND ALCOHOLISM**

DR. HAROLD VARMUS, DIRECTOR, NIH

**DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET,
DHHS**

OPENING REMARKS

Mr. PORTER. The subcommittee will come to order.

Today we are experimenting with a new format in our hearing process in which several institutes of the National Institutes of Health which support related research areas appear together as a panel. With us are the Neurology, Drug Abuse, Mental Health, and Alcoholism Institutes, all of whom are heavily involved in neuroscience research.

INTRODUCTION OF WITNESSES

Dr. Varmus, I understand you will begin with a few words about the commonality of the research portfolios of these four institutes, and then we will have a brief statement from each director, after which members can direct questions to the panel as well as the individual institute directors.

With us in addition to Dr. Varmus, the director of NIH, are Dr. Zach Hall, director of the National Institute of Neurological Disorders and Stroke; Dr. Stephen Hyman, the new director of the National Institute of Mental Health.

I understand Dr. Cowdry, who has served as our acting director, is with us also. He did such a fine job at NIMH. Welcome.

Dr. Alan Leshner, the director of the National Institute on Drug Abuse; and Dr. Enoch Gordis, director of the National Institute on Alcohol Abuse and Alcoholism.

We also welcome, as always, Dennis Williams. Dr. Varmus.

PANEL OPENING STATEMENT

Dr. VARMUS. Thank you, Mr. Porter.

As a result of discussions that you and I had earlier this year, we are conducting this experiment in the true spirit of NIH and the biomedical research process to tell you about some of the things that are going on at NIH in the area of neuroscience.

This is an experiment that reflects some of the goals of my own administration and stresses common themes in science and showcases the Institute Centers and Divisions working together as they pursue interests that are both unique to their own institutes and held in common.

Indeed, there are more than the four institutes represented here who are involved in neurosciences research. There are more than 10 institutes and centers that work in this area, an assembly of institutes which is reflected in the special interest groups in the intramural program that we described last Thursday, and reflected in a brain symposium that will be held next month under the sponsorship of the 11 institutes that work in this area.

Each of the institutes will spend 5 minutes presenting work recently conducted under its own aegis. But during the course of these discussions and during the question-and-answer period, you may want to pay special attention to three themes that we have identified as being held in common among the various institutes.

First, despite the very appreciable differences in the disorders under study by each of these institutes, you will find that these institutes and centers are trying to understand a single organ, the human brain, with a wide variety of experimental tools.

Secondly, you will find that in paying attention to the workings of the normal and the diseased brain, these institutes are uncovering both genetic and environmental factors that determine the normal workings of the brain and the diseases of the brain.

The third point you will appreciate is that a more fundamental understanding of the way in which the brain works as a biological entity is now driving clinical research. You will hear about how brain imaging is influencing diagnosis, how an understanding of receptors for neurotransmitters and for drugs of abuse are influencing, novel therapeutic strategies in a variety of areas.

Without further ado, we will listen to the four presentations, following which we will welcome your questions.

NINDS OPENING STATEMENT

Dr. HALL. Mr. Chairman and committee members, thank you for the opportunity to appear before this committee to describe how the Neurology Institute—NINDS—and the research that it sponsors is leading progress in understanding the brain and improving the health of Americans with disorders of the brain, spinal cord, and peripheral nerves.

I would like to begin by introducing Dr. Audrey Penn, who has recently joined the institute as deputy director. She comes to us from the Neurology Department at Columbia, where she has had a distinguished career as a clinician, a researcher, and an academic leader. She brings important talents to our institute, and we are delighted to have been able to lure her away from New York.

Last year I told this committee that we were on the verge of a new era in neurology and neurosurgery in which treatment of disorders of the brain would become the rule rather than the exception. This year I bring you dramatic new evidence for this assertion.

In December our institute announced the results of a clinical trial giving the first unequivocal evidence for a useful treatment for the most common form of stroke, the form in which a major brain artery is blocked.

To appreciate the importance of this finding, you must realize that until now stroke has been regarded as a disease for which prevention and rehabilitation were possible but for which there was essentially no treatment. NINDS clinical researchers have now found that a clot buster, t-PA, given within 3 hours after symptoms appear, can break up the clot and restore circulation to the brain. T-PA increases the chances of complete recovery for a victim of thrombotic stroke by 30 percent or more.

We estimate that up to 40,000 patients a year may experience functional recovery from stroke through the proper use of t-PA. The finding with t-PA is important in demonstrating that stroke, like a heart attack, is an emergency requiring acute treatment. The description of stroke as a brain attack captures this concept.

To realize the benefits of treating stroke as an emergency, patients, hospitals, and physicians must be educated to understand the importance of rapid response, a task that we at NINDS are working on in cooperation with patients and physician groups.

We believe that this new finding for stroke is but the tip of the iceberg and that more and more brain diseases will be found to be susceptible to treatment. In just the past few years we have seen new treatments for both multiple sclerosis and Lou Gehrig's disease, and as a result of progress in brain research we anticipate increased activity in clinical research. We see in that vein the new clinical center at NIH as a key component of this effort.

One of the most powerful tools for advancing knowledge about disease is molecular genetics, a theme that will be repeated by many of our colleagues throughout these hearings. Molecular genetics is particularly important for the nervous system as it is estimated that one-third of all genetic disorders result in brain disease.

This past year saw remarkable progress in the identification of brain disease genes. Among the most notable successes were the discovery of the genes for three rare childhood disorders, Batten disease, Friedreich's ataxia, and ataxia-telangiectasia, or AT.

AT, although rare, is of unusual significance in that carriers of a misspelled gene—that is, those with only one copy, who are estimated to be as many as 2 million in this country—may be at increased risk for cancer.

The discovery of the AT gene was the result of a joint project between an NINDS-supported researcher and the Center for Human Genome Research at NIH. You will hear more about this from Dr. Collins later.

Other genes that were discovered last year are linked to familial Alzheimer's disease, and in research sponsored by our institute and the Aging Institute, two related genes have been shown to be responsible for two distinct types of familial Alzheimer's disease.

Although the function of these genes is as yet unknown, alterations in them are suspected to lead to increased depositions of beta-amyloid protein, a protein that is thought to injure neurons and to cause the deficits that are found in Alzheimer's disease.

Finally, in our genetic progress, just last month a team of American and Finnish scientists cloned a gene that causes a severe progressive form of epilepsy. The gene encodes an enzyme that degrades other proteins. Although this particular enzyme was already known, its role in epilepsy was completely unsuspected, so that this finding will open an entirely new line of research on the causes of epilepsy and how it may be prevented and treated.

Finally, I would like to describe a recent advance in basic understanding of the brain that we believe will have important future implications for disease. Understanding the deficit in motor-sensitive and cognitive functions that arises in brain disease requires not only that we understand how the molecules and cells of the brain work but also that we understand how the billions of cells are organized into circuits that allow us to move, to perceive sensations, and to think and remember.

The task of understanding how this very large number of cells works together seems impossibly vast, but we have been aided by the development of sophisticated new techniques such as the imaging techniques that Dr. Varmus mentioned that allow us to observe the activity of large populations of cells and to analyze and predict their behaviors using computational methods.

One of the most remarkable discoveries that has been made is that the organization of the adult brain is more plastic, that is, more adaptable, than we had suspected. In fact, the current view is that some areas of the brain are in a continual state of reorganization based on the degree of use of different pathways in the brain.

Understanding how the brain adapts itself according to use offers the promise of providing help for those whose brains must reorganize as a result of disease or injury, such as patients recovering from stroke or from traumatic brain injury.

In closing, let me echo a theme mentioned by Dr. Varmus. I have been pleased since I have arrived at NIH about a year and a half ago to find a wide degree of cooperation among the various institutes and centers and divisions at the NIH concerned with brain disease. Although we are responsible for very different diseases and disorders, we each have a large stake in understanding how the brain works and collaborate extensively on particular problems and in various combinations. I look forward to working with my colleagues in this great endeavor.

Mr. Chairman, the funding year 1997 budget request for NINDS is \$671,148,000. I will be pleased to answer any questions that you might have.

[The prepared statement and biography of Dr. Zach Hall follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Neurological Disorders and Stroke

Mr. Chairman and Committee Members:

Thank you for the opportunity to appear before this Committee. I want to describe how NINDS research is leading to progress in understanding the brain and in improving the health of Americans with disorders of the brain, spinal cord and peripheral nerves. First, let me introduce Dr. Audrey Penn who has recently joined the NINDS as Deputy Director. Dr. Penn has come to us from Columbia University in New York, where she was a Professor of Neurology and a distinguished physician and researcher in neuroimmunology and neuromuscular disorders. I am also pleased to announce that we have a new Scientific Director, Dr. Story Landis, an outstanding developmental neurobiologist who has come from Case Western Reserve Medical School.

Research Accomplishments

Last year I told this Committee that we were on the verge of a new era in neurology and neurosurgery in which treatment of disorders of the brain would become the rule rather than the exception. This year I bring you dramatic new evidence for this change. In December of last year, NINDS announced the results of a clinical trial that provided the first unequivocal evidence for a useful treatment for the most common form of stroke in which a major brain artery is blocked. To appreciate the importance of this finding, you must realize that until now stroke has been regarded as a disease for which there were preventive measures and rehabilitative measures, but for which there was essentially no treatment. Using clinical observations and research on animals as a base, NINDS clinical trial investigators designed a multi-center trial to test the effects of a clot-buster, t-PA, given within three hours after the onset of symptoms, to break up the clot and restore circulation to the brain. The results were dramatic. For a victim of embolic stroke -- and there are up to 400,000 of them each year -- t-PA increases the chances of complete recovery by 30 percent or more. We estimate that up to 40,000 patients per year will recover from stroke through the proper use of t-PA. As stroke is the major cause of disability in adults, this finding will lessen the personal and financial burden of stroke for hundreds of thousands of Americans.

As I indicated above, this finding is important in a symbolic, as well as a substantive, way. It is part of a new concept that stroke, like a heart attack, is an emergency, requiring acute treatment. This idea is captured in the concept of stroke as "a brain attack." Recognizing the acute symptoms of stroke and treating it as an emergency requires a change in the behavior of patients, their doctors and the hospitals that treat them. The NINDS is now planning how it can contribute to education programs that will help bring this change about.

If diseases can be prevented, they don't have to be treated. A second important advance of the past year is a finding by NINDS-supported investigators that pregnant women can reduce the chance of birth defects in their children by monitoring their intake of vitamin A. The children of women who take very high levels of vitamin A--3 to 4 times the recommended daily allowance or RDA--before the seventh week of pregnancy have a higher level of birth defects. This risk can be reduced by maintaining vitamin A consumption at or near the current RDA.

Molecular genetics is one of the most powerful tools of modern biology. It is especially important for the investigation of brain diseases, which are estimated to comprise one third of all genetic disorders. This last year NINDS-supported investigators discovered the defective genes responsible for three rare neurological disorders and contributed to further understanding of the role of genes in Alzheimer's disease.

Ataxia-telangiectasia: An NINDS-supported scientist led an international team of investigators in the isolation of the gene for ataxia telangiectasia, a disease of children which is first expressed as a movement disorder. This very rare disorder is important because it affects many body systems. Children with this disease have an increased incidence of cancer, and are especially susceptible to infection. The AT gene may be a key to understanding signaling and control pathways that are involved in many other neurological diseases, cancers, and immune disorders.

Friedreich's Ataxia: Degeneration of the spinal cord and its connections to the brain affect several thousand people in the U.S. who have Friedreich's ataxia. Just weeks ago, investigators announced that they found that people with this disease have a trinucleotide repeat--a defect in which a portion of the genetic code is repeated more than a normal number of times. Friedreich's ataxia joins a growing list of neurological disorders, including Huntington's disease, in which this type of defect has been found. How the defect translates into disease, however, may differ among disorders, with evidence suggesting that other factors play a role in pathogenesis.

Batten disease: The neuronal ceroid lipofuscinoses (NCL) are fatal inherited disorders of the nervous system with onset usually in childhood. In 1995, significant advances were achieved with the discovery of the gene for infantile NCL and a different gene for juvenile NCL (Batten disease). A new project has been recently funded to search for the gene for a third form, late infantile NCL.

Alzheimer's disease: In the past year, scientists supported by the NIA and the NINDS found two additional genes linked to familial AD. The first discovery was the identification of a gene on chromosome 14 whose defects may cause up to 70 percent of the early onset form of dominantly inherited AD. The second gene, on chromosome 1, was identified in other families in which Alzheimer's disease is inherited. The two genes produce similar proteins whose exact functions are unknown, but which are suspected to lead to the increased production of the beta-amyloid protein whose accumulation is thought to damage neurons. The identification of these genes for familial AD should

foster a better understanding of the pathogenesis of both familial and sporadic AD, much as recent findings in familial breast cancer are leading to a better understanding of all breast cancer.

All together, the genes for more than fifty nervous system diseases have been discovered with hundreds remaining to be found. The identification of a gene provides new tools and ideas for further research. In some cases, gene discoveries may lead to new treatments. For example, building upon research conducted over decades at the NIH Clinical Center, gene transfer studies in patients with Gaucher's disease have now begun. This is a collaborative project between investigators in NINDS and NHLBI.

Brain Organization

The future understanding of cognitive deficits such as those seen in Alzheimer's disease will require that we understand not only the molecules and cells of the brain, but also how its billions of cells are organized into the circuits that allow us to move, to perceive sensations, and to think and remember. The task of understanding how all of these cells work together seems impossibly difficult, but we have been recently aided by the development of sophisticated new techniques that allow us to record the behavior of large populations of cells and to analyze and predict their behaviors using sophisticated computational techniques. Some of the results of these investigations are remarkable. One of the most important discoveries in recent years is that the organization of the adult brain is not static, as once thought, but is capable of change. In fact, the current view is that some parts of the brain are in a continual state of reorganization, so that pathways that are used more often have a larger representation in the brain. Understanding how the brain continually adapts itself offers the promise of providing help for those whose brains must reorganize as the result of disease or injury, such as patients recovering from traumatic brain injury or spinal cord injury or stroke.

Inter-ICD Collaborations

Neuroscience represents the most promising new frontier in research today. Because the brain interacts with every system of the body and its disorders affect people of all ages, there is widespread support for the neurosciences among the Institutes, centers, and divisions of the NIH. Because of our shared interests, extensive collaborative efforts exist among the agencies of the NIH concerned with brain research. This approach allows us to maximize the benefit of available resources and enhance the pursuit of the very best scientific opportunities. A major trans-NIH effort will involve at a minimum the NINDS, NIMH, NIAAA, NIDA, and NIA, to increase funds for research in the development of the nervous system, neuronal maintenance and repair, neurodegeneration, growth factors, and drug and alcohol addictions. For another example of a new collaborative effort, NINDS and the National Center for Human Genome Research have embarked on a genetic study of families affected by Parkinson's disease. Findings from this study may shed some light on the disease in its familial form as well as the more common sporadic cases.

Mr. Chairman, the FY 1997 budget request for this Institute is \$671,148,000. I would be pleased to answer any questions you might have.

Zach W. Hall, Ph.D.

Director, National Institute of Neurological Disorders and Stroke

EDUCATION:

B.A., Yale University, 1958; Emory School of Medicine, Emory University, 1958-1960; Department of Physiology, Emory University, 1960-1961; Ph.D., Biochemistry (Medical Sciences), Harvard University, 1966.

PROFESSIONAL HISTORY:

Director, National Institute of Neurological Disorders and Stroke, 1994 to present; Chief, Section on Synaptic Mechanisms, Laboratory of Cell Biology, Division of Intramural Research Programs, National Institute of Mental Health, 1994 to present; Head, Biomedical Sciences Graduate Program, University of California, San Francisco, 1992-1994; Jack and DeLoris Lange Professor of Physiology, University of California, San Francisco, 1992-1994; Chairman, Department of Physiology, University of California, San Francisco, 1987-1994; Head, Division of Neurobiology and Neuroscience Graduate Program, 1976-1988; Professor of Physiology, University of California, San Francisco, 1976-1994; Associate Professor, Harvard Medical School, Department of Neurobiology, 1972-1976; Assistant Professor, Harvard Medical School, Department of Neurobiology, 1968-1972; Fellow in Biochemistry, Stanford University, School of Medicine; 1966-1968.

PROFESSIONAL ORGANIZATIONS:

American Association for the Advancement of Science; American Society of Biological Chemists; American Society for Cell Biology; Society for Neuroscience; American Physiological Society; Society for General Physiologists; Scientific Advisory Committee for Neurobiology, Howard Hughes Medical Institute, 1992 to present; Graduate Fellowship Committee, Muscular Dystrophy Association, 1974-1982. Editorial Board, *Neuron*; Fachbeirat (Advisory Committee) Max-Planck Institute für experimentelle Medizin, Göttingen, 1994; Dana Foundation Alliance for the Decade of the Brain Initiative, 1992; Medical Advisory Board, Howard Hughes Medical Institute.

HONORS, AWARDS, FELLOWSHIPS:

Decade of the Brain Award, Congress of Neurological Surgeons, 1995; Honorary Member, American Neurological Association, 1995; Grass Lecturer, University of Miami, 1995; George Bishop Lecturer, Department of Neurology, Washington University, 1995; Grass Lecturer, University of Wisconsin, Milwaukee, 1994; Fellow, American Academy of Arts and Sciences, elected 1994; Alexander Forbes Lecturer, Grass Foundation, Marine Biological Laboratory, Woods Hole, Massachusetts, 1994; Jacob Javits Investigator in Neuroscience, 1993-1994; Steven Schuetze Lecturer, Columbia University, 1993; Lowell O. Randall Lecturer, Department of Pharmacology, University of Pennsylvania, 1991; Dunaway-Burnham Lecturer, Dartmouth Medical School, 1991; Grass Lecturer, SUNY, Albany, New York, 1984; Jacob Javits Investigator in Neuroscience, 1984-1991; Louis B. Flexner Lecturer, Institute for Neurological Sciences, University of Pennsylvania, 1984; William Evans Visiting Fellow, University of Otago, New Zealand, 1983; Grass Lecturer, University of North Carolina, 1978; Research Career Development Award, National Institute of Neurological Diseases and Stroke, 1972-1976; Fellow of the Medical Foundation, Inc., 1968-1970; Grass Foundation Fellow, Summer, 1961.

Mr. PORTER. Thank you, Dr. Hall.

Dr. Hyman, we are delighted to welcome you. As the new director of the National Institute of Mental Health, this is your first testimony before the subcommittee.

NIMH OPENING STATEMENT

Dr. HYMAN. Thank you for the welcome.

It is indeed my pleasure to appear before you for the first time to discuss the research programs of the National Institute of Mental Health. It is a privilege to present the NIMH programs in the company of colleagues who represent 4 of at least 10 NIH institutes who are interested in understanding the role of the brain in both health and in illness and also to highlight the unique contributions of NIMH to that endeavor.

NIMH MISSION

NIMH supports and conducts research to better understand, treat, and eventually to prevent mental disorders. There can be no doubt today that schizophrenia, manic depressive illness, major depression, obsessive compulsive disorder, and severe anxiety disorder are real diseases that affect the brain in specific and ascertainable ways. These severe conditions affect nearly 3 percent of adults, or some 5 million Americans.

The treatment of mental illness accounts for fully 10 percent of our Nation's annual health care bill, and this group of severe mental disorders accounts for nearly half of that. As a scientist, as a practicing physician, and now as NIMH director, I know all too well the tragedy of the diseases that confront us. But let me assure you that I am tremendously encouraged by the pace of our scientific progress.

Not long ago a severe mental disorder was, in effect, a life sentence. Almost nothing was known about the origins of these disorders, little existed in the way of effective treatments, and many families bore the cruel burden of stigma attached to a loved one's illness.

Yet by the time I entered psychiatric training and then began my research career, the air in many hospitals in which I worked literally began crackling with new hope because new medications had revolutionized our clinical practice and service delivery systems.

As importantly, the patients' responses to medication underscored the fact that mental disorders are indeed diseases of the brain, and this gave new impetus to our scientific mission.

The payoff of that defining mission was evident to me again last week when I met in the NIH Clinical Center with a young man who, despite available treatment, had been totally incapacitated by schizophrenia for 10 years. Today, as a result of receiving our newest medications, he has rejoined his family and is a functioning member of society. Indeed, he is even paying taxes.

I can tell you, as a physician, that our ability to help such a patient borders on the miraculous. At the beginning of my training just a short time ago, such a patient was literally consigned to the back wards of a mental hospital.

While the research that has helped him was indeed remarkable, we nonetheless must acknowledge that the best we can do is still not enough. Our treatments, while good, are far from perfect and thus clearly define our next challenge, to delve deeper into the study of the brain, exploiting new scientific opportunities and research capacities that have only recently come into existence.

NIMH PRIORITIES

Accordingly, over the next few years we will emphasize several priorities of which I will share three today and which were prefigured in Dr. Varmus' remarks. I believe that these are the kinds of themes that will enable us to realize the promise nearly within our grasp of vastly improving our ability to treat mental illness.

RESEARCH ON GENE/ENVIRONMENT INTERACTION

These priorities include, first, understanding the interaction of genes and environment in the origins of mental disorders. The stunning advances in molecular genetics in some neurologic disorders have made it possible to identify the genes responsible for devastating conditions ranging from Huntington's disease to cystic fibrosis.

While the same advanced molecular biological methods are used in psychiatric research and there have been a number of recent reports of potential chromosomal locations of vulnerability genes for mental disorders, NIMH has a unique challenge. We know already that vulnerability to any of the serious mental disorders is due not to single genes but to complex interactions of multiple genes and, in addition, does not result simply from the unfolding of genetic information. Diverse additional influences must interact with our genes to produce illness.

Because we do not know with certainty what the environmental risk factors are for mental disorders, we must look at factors that occur across the lifespan. Thus, our search extends from recent studies suggesting that prenatal or perinatal events, such as infection or malnutrition, might influence the development of schizophrenia in genetically vulnerable individuals, to evidence that points to streptococcal infection as a possible factor in the origins of some forms of obsessive compulsive disorders, to studies of how overwhelming life experience may provoke posttraumatic stress disorders.

MOVING BASIC RESEARCH TO CLINICAL USES

A second priority involves our own responsibilities for the knowledge that our science generates. First, we must devise ways to move new information about basic neurobiologic processes speedily into the realm of clinical application and, in turn, improve the means by which clinical insights guide our basic science. Understanding and optimizing this feedback loop in the evolution of our knowledge requires a focused program of what we might call "translational" research.

Let me note that the setting of a new NIH clinical center will help considerably with this feedback loop between basic and clinical research throughout the brain sciences.

A second facet of this priority requires that we be more creative and diligent in the task of integrating into a seamless whole the diverse data that NIMH science generates.

While there is widespread consensus that mental illnesses are just as real, as medically valid, as other brain disorders, a principal feature that differentiates both the diseases with which we are concerned as well as NIMH's scientific programs is the enormous span of information that we must deal with, literally from molecules to complex behavior. Our research programs at NIMH must take all of these into account. Achieving a coherent and clinically useful understanding from a research program of such breadth is an enormous integrative challenge.

DISSEMINATING RESEARCH KNOWLEDGE

Finally, I personally attach high priority to NIMH's accountability in communicating the fruits of our research to Congress; to health care providers, who are an especially important audience as we move to systems of managed care; and, most critically, to the American public, who make our work possible.

The fiscal year 1997 budget request for NIMH is \$578,149,000.

Thank you, Mr. Chairman. I will be pleased to answer any questions.

[The prepared statement and biography of Dr. Steven Hyman follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Mental Health

It is my pleasure to appear before you for the first time to discuss the research programs of the National Institute of Mental Health (NIMH).

Since the NIMH was authorized in 1946, its central mission has been to focus effective scientific research on understanding, treating, and preventing mental disorders. It is my privilege to have been appointed as Director of NIMH in the Institute's 50th Anniversary year, in an era when our Nation's half-century long investment in the study of these terrible and tragic diseases is yielding unprecedented dividends.

I have been asked by many individuals why, given NIMH's singular mission and focus on mental disorders, a molecular neuroscientist should lead the Institute. My answer is that right now spectacular scientific opportunities exist for understanding the basic components of nerve cells and how they work. That knowledge, integrated with NIMH's unique perspective on complex behaviors, will produce immense benefits for the attack on mental disorders. In essence, the ultimate challenge to NIMH research is to understand the integration of mind, body, and behavior — an integration that is mediated through the brain. I believe that I bring to the position of Director the necessary experience and commitment to achieving such an integrative balance — a balance that must influence all activities conducted under the NIMH aegis, from basic science to clinical research, to studies designed to enhance our service delivery system.

I step into the role of Director at a time of unprecedented scientific opportunity — opportunity that is based on an explosion of technical developments and new knowledge in many relevant areas of science that simply did not exist when the Congress originally sent forward legislation to authorize the NIMH as one of the earliest components of the NIH. These new areas or disciplines include molecular biology and molecular genetics, basic neuroscience, cognitive neuroscience, and human neuroimaging — that is, the ability to observe the brain think, imagine, and “feel” such emotions as fear and happiness, the hallucinations of psychosis encountered in severe mental illnesses, and the effects of cognitive and psychopharmacologic treatments on the brain disturbances associated with mental disorders.

My enthusiasm notwithstanding, I recognize that understanding the brain and its disorders may be the most complex scientific task ever undertaken by humanity. Yet, I believe that if we now capitalize on our best scientific opportunities in a disciplined and vigorous fashion, we can look forward to remarkable progress that will benefit patients with mental disorders and their families. Knowledge we acquire through research will expand our therapeutic capabilities, and, in turn, our increased understanding of the brain ills will have profound ramifications for removing the vestiges of stigma from mental disorders. Knowledge, not good intentions alone, will succeed in combating the

discrimination that persists in our service delivery and reimbursement policies, in aspects of medical education, in our communities, and even in our own families.

Let me draw on personal experience to attempt to describe the pace of progress in this field. When I embarked upon my medical residency training in psychiatry in 1981, I found a field in a state of transition. In some clinics and hospital units, patients with schizophrenia, manic depressive illness, obsessive compulsive disorder, and severe anxiety disorders were treated, appropriately, as patients suffering serious brain disorders, in just the way that one might have treated those suffering from stroke or brain tumor. The patients were approached in a non-moralizing professional fashion. They were treated with medications and/or psychotherapy as was appropriate and typically with considerable success. They and their families received education and support aimed at managing serious residual symptoms and detecting relapse at the earliest possible moment.

At the very same time, however, I observed other situations in which the families of patients with schizophrenia, for example, were treated as if *they* were the pathogens that had caused this terrible illness. Not to mention the tragic demoralization of these families, such a stance undermined the very purpose of treatment by alienating patients and families from each other and sometimes from care givers. At that early point in my career, I resolved to dedicate my life not only to understanding the brain in a way that would contribute to the treatment of mental disorders, but I also became determined to help others to appreciate the role of research in conquering illness. When well applied, the scientific method will fight the sources of stigma and, so importantly, give hope to individuals and families who for so long have been deprived of that most crucial resource.

We still do not know the precise etiology, or origins, of schizophrenia, manic depressive illness or other severe mental disorders. Nonetheless, the accumulating weight of the evidence — the great bulk of it resulting from NIMH-sponsored research — demonstrates that mental disorders *are* brain diseases. The difference between mental disorders and other brain disorders is that mental disorders, by definition, produce as their primary symptoms prominent derangements of thought, emotion, motivation, and complex behavior. For us to understand the causes of such disturbances demands the integrative perspective to which I referred.

This view of mental disorders does not imply a deterministic or pessimistic outlook. Much like medical disorders such as hypertension and diabetes, mental disorders are the result of intricate interactions between genetic vulnerabilities and environmental influences. Our aim is to understand the processes by which mental disorders occur in order to develop more effective and definitive treatments and, ultimately, to prevent these conditions.

What evidence ties mental disorders to the brain? Let me give you some examples. Through NIMH-supported research, we now know that individuals with schizophrenia have abnormalities in the size of their cerebral ventricles, those fluid-filled cavities in the brain; simply put, in schizophrenia, we see irregularities in the ratio of

brain tissue to fluid in the brain. NIMH-sponsored research also has provided compelling evidence that the connections of nerve cells in the brain, the circuits that underlie the processing of thoughts and emotions, do not develop or function normally in patients with schizophrenia. This information is derived from post-mortem studies of the brains of individuals with schizophrenia and from noninvasive neuroimaging. These scientific techniques demonstrate beyond doubt that schizophrenia is a primary brain disorder.

I am pleased to report that steady progress is being made in understanding the genetic vulnerabilities of schizophrenia, manic depressive illness and other major mental disorders. Earlier this month, the prestigious journal, Nature Genetics, reported findings, from three separate research teams, about the search for the genes responsible for manic depressive illness. Two of these projects were conducted by NIMH-supported scientists — one team led by an intramural scientist, and one composed of extramural investigators. Let me hasten to note that this research apparently did not identify a specific responsible gene or genes. Indeed, these three sophisticated studies, all working with diverse, adequately sized populations, zeroed in on different chromosomes. Yet, far from being discouraged by what might appear to be conflicting findings, I am buoyed by the results, for they quite clearly suggest next steps for molecular genetics studies of psychiatric disorders. Let me explain.

The major psychiatric disorders are likely to prove complex since it appears that even within a single *individual* more than one gene may contribute to a particular illness or disorder. These disorders, moreover, possess an additional layer of complexity in contrast to diseases such as Huntington's Disease or cystic fibrosis wherein the presence of a single gene ensures that a person will have the illness. That is, in mental disorders, genes confer *vulnerability* rather than the certainty of developing the disorder. The clearest clinical evidence for heritability of any disease comes from the study of identical twins — that is, twins with one hundred percent of their genes in common. In the case of Huntington's Disease, if one twin is affected, the other, should he or she live long enough, inevitably will develop Huntington's Disease. In contrast, if one twin were to develop schizophrenia, the co-twin would have approximately a fifty percent chance of developing the illness. The lack of a certain, or 100-percent match, means that genes and environmental forces interact to produce schizophrenia. For manic depressive illness, the relative contribution of genes compared to environmental influences appears to be higher, but still is not one hundred percent.

From a research perspective, this information has an extremely important implication. It is often thought that genetic, or "biological," research and behavioral research are somehow competitive with each other, or mutually exclusive. In fact, mental illnesses are manifested as behavioral changes. The eventual discovery of genes that produce vulnerability to mental disorders will initiate a new era in the integration of neuroscience, behavioral research, and prevention research. And I can assure you that only a research program with the breadth of perspective to seek the links between seemingly disparate areas of inquiry will sharpen our capabilities to understand which environmental factors interact in what ways with vulnerability genes to produce disease.

I should point out we have no certainty as to what the salient, or pertinent, environmental risks are for mental disorders: To identify those, we must think broadly. Important environmental factors may include pre- or perinatal injuries or infections, subsequent illnesses, or, as is clearest in the case of posttraumatic stress disorder, overwhelming life experiences. Investigation of these various factors is a scientific and medical imperative, and NIMH thus will continue to support relevant basic behavioral and biological science.

I am aware that the breadth of NIMH's basic research portfolio has been questioned in recent years. I see this as a challenge for the Institute to articulate more clearly why scientists take certain approaches, or use particular animal models for studies of complex behaviors. I look forward to the opportunities the Institute will have to help people outside our scientific fields understand and appreciate how basic science is, indeed, the lifeblood of clinical science and improved clinical care.

One step that NIMH will take toward the goal of ensuring the best "fit" between basic and clinical research needs already is in motion. My predecessor and colleague, Dr. Rex Cowdry, recently convened a Blue Ribbon Panel of scientist/administrators from the extramural community and from other intramural components of NIH to examine the NIMH Intramural Research Program in its entirety. By the end of this calendar year, I expect to be able to act on recommendations this Planning Committee develops. The goal is to optimize our Intramural program's unique resources while assuring the highest quality science. In this context, the planned refurbishment of the NIH Clinical Center offers an opportunity to regroup all NIMH intramural research on the Bethesda campus. This is substantively important for our scientists, and will ensure all Americans that basic as well as clinical research on mental disorders is truly and fundamentally a part of the NIH's scientific mainstream.

I have spoken thus far about the ways in which NIMH-sponsored advances in brain research will contribute to treatments and to prevention, and at the same time to the destigmatization of mental disorders among care givers and society at large. However, individuals with mental disorders currently face a different type of discrimination, one that is related to the status of mental disorders in health insurance. While I understand the importance of keeping overall health care costs within bounds, I can state without reservation that research shows no biomedical justification for differentiating serious mental illness from other serious and potentially chronic disorders of the nervous system such as stroke, brain tumor, or paralysis. There is absolutely no biomedical justification for policies that judge mental disorders as being in any way less real or less deserving of treatment, and an extensive body of rigorous research has demonstrated that treatment for the severe mental illnesses is both precise and cost-effective. Given the early age of onset of many mental disorders, with their remarkably serious repercussions for developing lives and, in turn, for the long-term productivity of members of our society, the need for access to treatment seems particularly acute. In light of the staggering annual costs of mental illness to the Nation — \$148 billion is the most recent estimate — we also will be working to strengthen the already compelling evidence that the timely and appropriate diagnosis, treatment, and, when possible, prevention of mental illnesses can play a critical role in reducing the

Nation's health care bill. I take very seriously the role of NIMH-supported treatment and services research in demonstrating the efficacy and cost effectiveness of the treatment so that we can facilitate the rapid reintegration of care for those with serious mental disorders into the mainstream of American health care.

The fiscal year 1997 budget request for NIMH is \$578,149,000. Thank you Mr. Chairman. I will be pleased to answer any questions.

**CURRICULUM VITAE
STEVEN EDWARD HYMAN, M.D.**

EDUCATION:

- 1974: B.A. - Yale University (Summa Cum Laude)
 1976: B.A. (Honors), M.A., University of Cambridge, England
 1980: M.D., Harvard Medical School (Cum Laude)

LICENSED to practice Medicine, Massachusetts.

CERTIFICATION, the American Board, Psychiatry, 1986

POSTDOCTORAL TRAINING

- 1980-1981 Intern in Medicine, Massachusetts General Hospital (MGH)
 1981-1984 Resident in Psychiatry, McLean Hospital
 Chief Resident, McLean Hospital (1982)
 1983-1984 Clinical and Research Fellow in Medicine (Endocrinology) and
 Neurology, MGH
 1984-1988 Research Fellow in Molecular Biology, MGH

ACADEMIC APPOINTMENTS

- 1980-1981: Clinical Fellow in Medicine, Harvard Medical School (HMS)
 1981-1984 Clinical Fellow in Psychiatry, HMS
 1984-1987 Research Fellow in Genetics, HMS
 1987-1989 Instructor in Psychiatry, HMS
 1989-1992 Assistant Professor of Psychiatry, HMS
 1993-: Associate Professor of Psychiatry, HMS

HOSPITAL APPOINTMENTS

- 1984-1988 Fellow in Molecular Biology, MGH
 1989 Assistant in Psychiatry, MGH
 1990-1994 Assistant Psychiatry, MGH
 1995-: Associate Psychiatrist, MGH

PROFESSIONAL APPOINTMENTS:

- 1990-: Director of Research, Massachusetts General Hospital
 1992-1995 Director, Division on Addictions, Harvard Medical School
 1994-: Director, Harvard University Interfaculty Initiative on
 Mind/Brain/Behavior
 1996-: Director, National Institute of Mental Health

AWARDS AND HONORS

- 1974 Distinction in Philosophy, Major, and in History, the Arts, and
 Letters, Yale University
 1974-1976 Mellon Fellowship, University of Cambridge, Cambridge,
 England
 1980 Soma Weiss Assembly, Harvard Medical School
 1983-1984 Dupont-Warren Fellowship, Department of Psychiatry,
 Harvard Medical School
 1983 Laughlin Fellowship, American College of Psychiatry

Steven E. Hyman, M.D.

1984	Laughlin Award of the National Psychiatric Endowment Fund
1985-1990	Physician Scientist Award, (NIH/NIDDK)
1988-1993	First Independent Research Support and Transition (FIRST) Award (NIH/NIMH)
1990-1995	Research Scientist Development Award, Level 2 (NIH/NIMH)
1994-:	Research Program Project Grant (NIH/NIDA)
1995-:	Research Program Project Grant (NIH/NIDA)
1995-:	Research Project Grant (RO1), (NIH/NIDA)
1995-:	Research Project Grant (RO1), (NIH/NINDS)
1995-:	Research Scientist Development Award, Level 2 (NIH/NIDA)

COMMITTEE ASSIGNMENTS, NATIONAL

1986-1991	Ad Hoc member, Research Scientist Development Committee, NIMH
1988	Special Review Committees, NIMH
1991-1994	Public Information Committee, Society for Neuroscience
1992	External Advisory Committee, NINDS Program Project on Basal Ganglia and Parkinsonism, University of Pittsburgh
1995	Program Committee, Society for Neuroscience
1995	Special Review Committees, NIDA

EDITORIAL BOARDS

1987-	Journal of Geriatric Psychiatry and Neurology
1988-	Psychosomatics
1992-	Harvard Review of Psychiatry
1992-	Neuropsychiatric Genetics (Section of American Journal of Medical Genetics)
1994-	Journal of Neurochemistry
1996-	Archives of General Psychiatry

PROFESSIONAL SOCIETIES

1984-	American Psychiatric Association
1986-	Society for Neuroscience
1991-	Boston Society of Neurology and Psychiatry

Mr. PORTER. Thank you, Dr. Hyman.
Dr. Leshner.

NIDA OPENING STATEMENT

Dr. LESHNER. Mr. Chairman, this year has once again seen extraordinary progress in drug abuse research. I want to start by thanking the administration and the Congress and this subcommittee in particular for your strong support of the NIH. Your confidence has permitted NIDA to continue escalating the pace of discovery and understanding and dealing with drug abuse and addiction.

The National Institute on Drug Abuse supports over 85 percent of the world's drug abuse research. Because we represent such a great proportion of the research effort, we recognize that just doing good science isn't enough. It is vital that this information be actively disseminated to the families, communities, practitioners, and policymakers who so urgently need it, and we are doing just that.

As one example, we have just come from the first of a new series of NIDA town meetings around the country that are designed to foster information dissemination.

Today I want to give you a few examples of just how far we have come, beginning with our understanding of the role of the brain and drug addiction. I will use these posters to illustrate my first few examples.

The first poster shows, as the ads say, one's brain on drugs. This poster shows the way cocaine is taken up into the brain, into the precise sites where it exerts many of its stimulating effects.

What you are seeing here in the yellow areas is radioactive cocaine actually being taken up into a human's brain as minutes pass. You are seeing the same brain slice recorded by PET scan every few minutes in a time series.

We no longer need to use inexact metaphors like "fried brains" to indicate how drugs affect and modify people's brains; we have the scientific knowledge to do that. We have now identified the brain receptors and mechanisms of action for every major drug of abuse.

The second poster compares the brain of a normal non-drug-taking individual with the brain of a chronic cocaine user who has stopped taking the drug, an addict who is no longer taking the drug. As you can see, after 10 days or even 100 days of abstinence, the persistent depressive effects of drug use on metabolic activity are still apparent. Prolonged drug use produces profound changes in brain function that last long after one stops using the drug.

The third poster shows the memory of drugs, or, more specifically, one precise area of the brain where the memory of the drug experience and craving seems to occur. In this chart, in the right panel, you see tremendous activity in white in the amygdala, the brain area involved in memories of conditioned or learned emotional responses. This activation is caused by mere exposure to cues that have come to be associated with or conditioned to cocaine use, like drug paraphernalia. No actual drugs are involved here. This addict has only been shown drug paraphernalia.

Importantly, this brain area is being activated at the same time that the subject experiences tremendous drug craving in response to exposure to those same learned cues.

Compare this brain scan with the scan on the left when the same individual was exposed to neutral stimuli that did not elicit craving and where there is no activation in the amygdala.

What you have seen in these three posters is, first, your brain on drugs, then your brain after drugs, and then the memory of drugs.

This past year has also seen a variety of major basic science advances that are helping move us much more quickly toward our top priority goal of developing effective treatment medications for cocaine addiction, for which we now have no medications. These kinds of findings are a major breakthrough because they provide clear biological targets at which to direct our anticocaine medication development efforts.

As one example, this year NIDA-supported researchers successfully immunized animals against the stimulant effects of cocaine. As another example, NIDA-supported researchers have recently shown that activation in the brain of one type of dopamine receptor, the D-1 receptor, suppresses drug-seeking behavior, whereas activation of the D-2 receptor stimulates drug seeking. Thus, D-1 agonist compounds may be good candidates as anticocaine medications.

We have also continued to make significant progress in identifying effective nonpharmacological behavioral treatments. We are very pleased to see the clear emergence in the past few years of new and quite effective treatment by cognitive behavioral therapies and contingency management.

NIDA also devotes substantial efforts to the intersection between drug abuse and HIV/AIDS. Drug abuse directly or indirectly is now the fastest growing vector for the spread of HIV. NIDA-supported research spans all aspects of the intersection between these two now inextricably linked epidemics. As just one example, NIDA-supported researchers have developed outreach and intervention strategies that are very effective in changing risk behaviors associated with the spread of HIV. In one recent study of over 9,000 drug users who were not in treatment at the time, the intervention resulted in 36 percent of the subjects actually stopping their drug use, and of those who continued to use drugs, 35 percent substantially changed their high-risk drug use patterns. This is substantial behavior change for 58 percent of the subjects.

Mr. Chairman, as these few examples show, the findings of drug abuse research have presented us with unprecedented opportunities to understand and to respond to the challenge of drug addiction. To continue this progress, NIDA requests \$312,014,000 for fiscal year 1997.

Thank you. I will be pleased to answer any questions.

[The prepared statement and biography of Dr. Alan Leshner follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Drug Abuse

Mr. Chairman and Members of the Subcommittee, I am delighted to be here today. This year has seen extraordinary progress in drug abuse research. I at last can say with confidence that we are now in the early but very hopeful stages of seeing the results of fundamental brain research translated into new kinds of treatments for both heroin and cocaine addiction. I want to thank both the Administration and the Congress - and this Subcommittee in particular - for supporting research programs at the National Institutes of Health (NIH). Your confidence has permitted the National Institute on Drug Abuse (NIDA) to continue escalating the pace of discovery in understanding drug addiction.

Mr. Chairman, NIDA supports over 85 percent of the world's drug abuse research - research that has totally revolutionized our understanding of addiction. We also recognize that doing good science is not enough. It is vital that this information be disseminated to the families, communities, practitioners and policy makers who so urgently need it. And we are doing just that. In fact, we have just come back from the first of a series of town meetings around the country designed to foster information exchange among educators, health care providers, State and local anti-drug coalitions, and civic organizations, as well as researchers. These meetings will help ensure that NIDA-supported research is both useful and used.

Before I go on with my statement, I would like to show you how much we now understand about the role of the brain in drug addiction. The first chart literally shows your brain on drugs, showing the way cocaine is taken up into the base of the brain, where it exerts many of its stimulating effects [Figure 1]. The second chart compares the brain of a normal individual with that of a chronic drug user, even after 10 and 100 days of abstinence. This shows the persistent effects of drug use that last long after the addict has stopped using drugs [Figure 2]. Finally, the third poster shows the MEMORY of drugs - or more specifically the precise areas of the brain where the memory of the drug experience and craving seem to be [Figure 3]. We not only are identifying where in the brain addiction takes place, but we are repeatedly seeing that there is a common essence to all addictions. That is, there are certain physiological, pharmacological and anatomical substrates that are always present regardless of the addictive substance.

The progress of the past year has continued to move us dramatically forward in our understanding of addiction. Among the most remarkable accomplishments of the past year is the successful immunization of animals against the psychostimulant effects of cocaine [Figure 4]. These results are an exciting breakthrough in NIDA's efforts to develop an anti-cocaine agent for the treatment of cocaine addiction.

We have also made substantial progress on other fronts in our efforts to develop an effective medication for the treatment of cocaine addiction. For example, NIDA researchers have recently shown that activation in the brain of one type of dopamine receptor, the D1,

suppresses drug-seeking behavior and relapse, whereas activation of another, the D2, triggers drug-seeking behavior. Studies such as these are critical in directing our efforts to identify potential anti-cocaine medications.

One of NIDA's most important areas of research has been the identification of the neurobiological bases of all aspects of addiction, including craving. Drug craving is one of the major factors that can precipitate relapse. A recent study, using PET brain imaging, has identified specific regions in the brain that are particularly active during cocaine craving. This and other studies are presenting us with unprecedented opportunities to determine the neurobiological mechanisms of craving, which can lead to the development of treatments that might prevent or reduce craving.

NIDA-supported researchers have also made great strides in our understanding of the brain's opiate system and its role in addiction. Recently, NIDA researchers have shown that opioid peptides may be involved in nicotine dependence and that the mu opiate receptor may be involved in cocaine craving. These discoveries support the hypothesis that the opioid system may play a fundamental role in the addiction to a variety of drugs, and they underscore the importance of determining the precise neurobiological mechanisms involved in addiction. They also provide additional avenues of research in our efforts to develop effective medications for the treatment of addictions.

Employing the most sophisticated molecular and cellular biology techniques, NIDA-supported research has shown us that drug use can cause relatively permanent changes in brain structure and function, many of which are involved in the phenomenon of addiction. We have identified changes in overall neurotransmitter levels in critical brain regions, and in molecular and cellular events within individual cells. Most recently, NIDA researchers have shown that MDMA (ecstasy) causes the degeneration of nerve axons and terminals in the brain. Although these axons and terminals may regrow, they do not grow back normally. A separate NIDA study has shown that prenatal exposure to cocaine causes severe disruptions in the normal structure of the cerebral cortex of the newborn infant and a decrease in the number of neurons and nonneuronal cells. Studies such as these are helping us to better understand how drugs alter the brain and how we might ameliorate some of these devastating effects.

In another domain, we have identified ways in which the neurobiological effects of heavy drug use may impact functioning. College students who were heavy marijuana users were found to have significant impairments in a variety of measures of intellectual functioning that lasted at least 24 hours after their last drug use. This kind of finding is very important to our prevention efforts, because it dispels the myth that once one stops using a drug like marijuana, its effects are gone very quickly.

NIDA researchers have also made significant progress in efforts to identify effective nonpharmacological treatments, as well as medications. For example, NIDA researchers have demonstrated that managing contingencies, or a variety of incentives, is effective in reducing drug use. In these studies, subjects received vouchers for goods and services that increased as the number of drug-free days increased. The vouchers could be exchanged for goods and services that were considered consistent with the subject's treatment goals. The use of

vouchers resulted in a significant drop in drug use, showing that voucher-based reinforcement contingencies can produce sustained abstinence from drug use. Since this type of contingency management greatly reduced injection drug use, vouchers may also be a valuable tool for reducing the spread of HIV.

Recognizing education and prevention programs as essential components in the fight against drug abuse and addiction, NIDA has continued its efforts to develop effective drug use prevention strategies. NIDA-funded studies have clearly demonstrated that a major protective factor in preventing drug use among children is parental involvement in the life of the child. Studies have shown that this involvement needs to be sustained and multifaceted, that is, parents need to be involved in all aspects of their children's lives.

In addition to parental involvement, a long-term NIDA-funded study has demonstrated that school based prevention programs can be highly effective in reducing drug use by teenagers over a sustained period of time. This prevention program started children at early ages, combined training in the skills and knowledge to resist social pressure to use drugs and in basic interpersonal skills with information about the risks and prevalence of drug abuse, and, included booster sessions. Lower levels of tobacco, alcohol and marijuana use were seen among teens participating in the program, and these reductions were still evident at the time of graduation.

NIDA has also made significant strides in research focused on identifying, studying, and modifying drug-use behaviors that increase HIV transmission risks among people who are in- and out-of-treatment. Understanding the link between drug abuse and the transmission of HIV has become even more critical in light of the transformation of AIDS from a disease that is primarily found in gay white men to one that is primarily a disease of drug abusers and their often non-drug-using family members, sexual partners, and children, to whom they transmit the disease. Indeed, 55 percent of pediatric AIDS cases are among children born to mothers who themselves injected drugs or had contact with an injecting drug user. Recent CDC findings show that as of June 1995, approximately 3 in 8 cases of AIDS were related to injection drug use. NIDA-funded studies have demonstrated that significant and long-term reductions in HIV risk behaviors can be obtained when addicts are treated. Importantly, and for some counter-intuitively, NIDA-supported studies have also repeatedly shown that people still using drugs intravenously are nonetheless amenable to behavior change strategies. For example, major NIDA-funded studies have now clearly demonstrated that street-based outreach, including HIV counseling and testing, leads to dramatic decreases in HIV needle-related risk behaviors among out-of-treatment drug users.

These are but a few of the many exciting discoveries in drug abuse research that have been made in the past year. These discoveries and others have set the stage for what I anticipate will be yet another incredible year of drug abuse research. We are now even closer to NIDA's top priority of developing an anti-cocaine medication. During the coming year we will continue to aggressively work towards this goal. Advanced technologies are now available for rapidly screening hundreds of thousands of chemicals for their ability to block the action of cocaine at the dopamine uptake site. NIDA will use these technologies and others to screen for an anti-cocaine agent. We have already identified several compounds that

are extremely potent and highly selective for the dopamine transporter - among these may be an effective treatment for cocaine addiction.

NIDA will also continue to actively pursue strategies that enlist the body's own natural defenses to combat cocaine. The successful immunization of animals against the psychostimulant effects of cocaine is an exciting first step in designing immunological tools for the treatment of cocaine addiction. NIDA is also pursuing the development of antibodies that recognize cocaine and metabolize it to harmless breakdown products before it can reach the brain. In the coming year, these novel approaches to medications development will be an integral part of NIDA's ongoing efforts to develop effective medications for the treatment of cocaine addiction.

NIDA will also move forward with research programs to develop, refine and use increasingly sophisticated molecular tools to better understand the process of addiction. For example, scientists have recently genetically knocked out the dopamine reuptake transporter. This valuable new tool will be extremely useful to NIDA-funded researchers for understanding how cocaine and amphetamine act in the brain. NIDA is also beginning to support investigations of even more sophisticated molecular biological tools, such as "conditional knockouts" which may permit time and tissue-specific regulation of gene function. Tools such as these are helping to revolutionize our understanding of the neurobiological bases of addiction and should greatly facilitate our efforts to develop effective treatments for all aspects of addiction.

The increasing linkage of HIV/AIDS to drug abuse makes it even more critical that NIDA also focus substantial research effort on developing effective interventions to reduce high risk behaviors among drug abusers. There is also a critical need to examine the spectrum of HIV disease in adolescents, particularly those who abuse illicit drugs. NIDA has also initiated studies to improve HIV treatment in pregnant and non-pregnant drug-using women. These studies are especially important in light of a NIDA-funded study documenting that 73% of HIV-infected drug-using women do not receive adequate prenatal care and studies that show that AZT significantly reduces maternal-child transmission of HIV.

Medical care access and utilization historically have been inadequate among drug abusers. To address this, in the coming year, NIDA will fund studies to develop models and strategies for linking drug abuse treatment with primary medical care. Special attention will be paid to the effects on the prevention, incidence, and progression of medical disorders in drug abusing populations and the cost and effectiveness of linked treatment.

NIDA will also expand its research on risk and resilience factors which influence an individual's drug involvement. Research will focus on family function and parenting, early problematic childhood characteristics, psychological skills enhancement, and neighborhood factors that influence social norms and childhood expectations. This research on family-child-neighborhood risk and resilience factors is poised to interface with studies on special vulnerabilities associated with drug use and escalation to dependence.

Mr. Chairman, the findings of drug abuse research have presented us with unprecedented opportunities to understand and treat addiction. As we move into the 21st century, we will see new mind-altering and addicting drugs. Our increasing knowledge of the brain and behavior will allow us to respond to these new challenges. To accomplish this, NIDA requests \$312,014,000 for FY 1997. Thank you, Mr. Chairman. I would be pleased to answer any questions.

ALAN I. LESHNER

*Director
National Institute on Drug Abuse
National Institutes of Health*

Dr. Leshner was appointed Director of the National Institute on Drug Abuse (NIDA) in February 1994. One of the scientific institutes of the U.S. National Institutes of Health, NIDA supports over 85% of the world's research on the health aspects of drug abuse and addiction. The Institute also carries out a large variety of programs to ensure the rapid dissemination and use in both practice and policy settings of the results of the research it supports.

Prior to coming to NIDA, Dr. Leshner had been the Deputy Director of the National Institute of Mental Health since 1988. He also served as Acting Director of the NIMH from 1990 to 1992. Dr. Leshner went to NIMH from the National Science Foundation (NSF), where he held a variety of senior positions, focusing on basic research in the biological, behavioral and social sciences, and on science education.

Dr. Leshner went to NSF after 10 years at Bucknell University, where he was Professor of Psychology. While on the faculty at Bucknell, he also held long-term visiting appointments at the Postgraduate Medical School in Budapest, Hungary, at the Wisconsin Regional Primate Research Center, and as a Fulbright Scholar at the Weizmann Institute of Science in Israel. Dr. Leshner's research has focused on the biological bases of behavior. He is the author of a major textbook on the relationship between hormones and behavior, and numerous book chapters and papers in professional journals. He also has published extensively in the areas of science and technology policy and education.

Dr. Leshner received his undergraduate degree in psychology from Franklin and Marshall College, and the M.S. and Ph. D. degrees in physiological psychology from Rutgers University. He has been elected a fellow of many professional societies, and he has received numerous awards from both professional and lay groups for his national leadership in science, mental illness and mental health, and substance abuse and addiction.

Mr. PORTER. Thank you.
Dr. Gordis.

NIAAA OPENING STATEMENT

Dr. GORDIS. Thank you, Mr. Chairman. My colleagues and I at the NIAAA are pleased to present advances in research during the last few years and to tell you of some of our plans for the future.

Before I begin, I would like to introduce our deputy director of the NIAAA, Dr. Mary Dufour.

I think you will see from the points that I make during the next few minutes that the themes that Dr. Varmus has raised—that is, the fundamental aspects of neuroscience, the fact that both genes and environment play a role in the disease that we study, and that clinical research is impacted on very heavily by neuroscience—will become quite evident.

Alcohol is a legal substance used safely and with pleasure by most people who use it. But for the 15 million or so people who abuse it or are alcoholics, it costs the country about \$100 billion a year, 100,000 deaths, and 20 to 40 percent of adult hospital beds in urban centers that are occupied by people there for the consequences of their drinking.

The questions we are trying to answer have to do with: What happens in the brain that some people become addicted? What is the nature of their vulnerability? Why is it that only a minority of people become addicted to alcohol and most do not? How does alcohol cause damage to various organs? How can we improve treatment? And how can we prevent these problems?

To understand the process of addiction, which means the development of craving, of withdrawal, of tolerance, and physical dependence, we use all the modern tools of neuroscience which have been mentioned today—imaging, neurochemistry, and the study of brain circuits in various ways. These in turn, are linked to the vulnerability issue, because some of the structural changes of the brain that we find before people have started to drink obviously are connected with their vulnerability.

GENETICS

The vulnerability to alcoholism is a difficult issue. We are dealing with a behavioral disorder which is undoubtedly polygenic. This means that it is not a single gene that causes alcoholism, but many genes influence it. At the same time there are strong environmental influences.

We know from twin and adoption studies that there is a heavy genetic influence on the vulnerability to alcoholism. We also know from animal studies that changes in child-rearing habits have an effect on later drinking in these animals, which undoubtedly reflects the effects of the environment on the brain, the issue of plasticity mentioned by several speakers.

The major collaborative study on the genetics of alcoholism is coming to its final years now. Almost 300 informative families are ready for final study. Blood drawn from the members is in two repositories. We are ready to begin the study of the linkage and the

pair analysis over the next 2 years, and we believe that in the next few months the first findings will be announced.

An important study by one of our investigators, Dr. Marc Schuckitt, has shown that the mere sensitivity to alcohol at the age of 20 is highly predictive of developing alcoholism at the age of 30. What this depends upon in the genetic sense is something that we will be looking at carefully.

The payoff for genetic research is new pharmacotherapy, better prevention, and a better understanding of what the role of environment is as a result of precise understanding of the role of the genes.

MEDICAL CONSEQUENCES

Important advances are being made in understanding liver and heart damage, the influence of alcohol on certain cancers, and the issue of fetal alcohol syndrome. The heart issue is complex because low doses of alcohol have a coronary protective effect. Higher doses cause heart disease, including cardiomyopathy, and other complications.

TREATMENT

One of the fruits of neuroscience research is the development of Naltrexone, the first new therapy for alcoholism in the last 40 years. We are moving ahead by studying its mechanism of action and with subsets of patients who respond to it better than others.

Both the extramural and the intramural work on the treatment of alcoholism benefit greatly from the work conducted by our intramural program at the clinical center. Verbal therapy is also important, and our 1,700-patient study of treatment matching is now complete, and the results are being prepared for publication. The future era in treatment for the next 10 or 15 years will be a mix of both verbal and pharmacologic therapies.

Prevention research is making significant advances. I will mention the important effect of NIAAA research on zero tolerance, and on the 21-year-old age for driving. These policies save hundreds of young people's lives.

As you can see, the themes that Dr. Varmus raised—brain science, genes and environment, and clinical research—are all very germane to the work that we do at NIAAA. Our research spans the distance between cells and all society.

I will be pleased to answer any questions.

The budget request for the fiscal year 1997 is \$192,280,000.

[The prepared statement and biography of Dr. Enoch Gordis follow:]

DEPARTMENT OF HEALTH OF HUMAN SERVICES

National Institutes of Health

Statement of the Director

National Institute on Alcohol Abuse and Alcoholism

Mr. Chairman and Members of the Committee:

I am pleased to be here with you today to discuss the many scientific advances and research opportunities at the National Institute on Alcohol Abuse and Alcoholism (NIAAA). NIAAA is leading the nation in alcohol research by supporting investigations directed at improving the prevention and treatment of alcohol abuse and alcoholism. Alcohol misuse is involved in about one-half of all homicides and serious assaults, one-third of suicides and accidental deaths, and a high proportion of robberies and incidents of domestic violence. Alcohol abuse and alcoholism exact tolls of approximately \$98.6 billion dollars annually and our health care system registers the repercussions of this major problem. Up to 40 percent of patients in urban hospital beds are there for treatment of conditions caused by alcohol abuse and alcoholism.

The NIAAA-sponsored research seeks to answer why it is that millions of otherwise intelligent and dependable people cannot stop abusive drinking even though they know they are killing themselves? How can we better prevent alcohol problems, and if they occur, treat them better and reverse their consequences? How does alcohol damage organs? Answers to these questions will lead to better prevention efforts and treatments for alcoholism, as well as, better understanding of the damage caused by alcohol to the brain and other organs.

Alcohol, after ingestion, is distributed to every cell in the body. Yet it produces very specific effects: motor impairment, memory loss, and the possible development of alcohol addiction, or alcoholism. One of NIAAA's priority areas is research on neuroscience that will determine what happens in the brain when people drink alcohol and how alcohol effects the brain. This research will help us understand which brain cells, neurotransmitters, and connected neurons account for the specific action of alcohol and the symptoms of alcoholism: physical dependence, tolerance, loss of control of drinking, and the craving for alcohol seen in sober alcoholics which leads to relapse. This state-of-the-art neuroscience research is being conducted in our intramural program, as well as being supported extramurally.

The NIAAA is supporting projects that are making use of the most advanced technology available to address these issues. For example, receptor studies, imaging, and brain wave analysis are a few of these cutting-edge technologies that may lead to better predictive tools. One such predictive tool may be brain neuroelectrical activity--brain waves. A considerable body of evidence suggests that brain wave patterns, including event-related potentials, are heritable. Recently, studies have found evidence for a major gene controlling the familial similarity found in brainwaves. If future studies confirm these findings in larger sample sizes, clinicians will have a biological marker for identifying individuals, as well as groups, who are at greatest risk

of developing alcoholism. This heralds an opportunity to break the intergenerational cycle in families predisposed to developing alcoholism.

To understand why some people are especially vulnerable to alcoholism, NIAAA is also coordinating a multi-disciplinary collaborative research study, the Cooperative Agreements on the Genetics of Alcoholism (COGA), designed to investigate the genetics of alcoholism. The goal of this research is to find the genes in alcoholics that account for that portion of vulnerability that is inherited. By looking at these families, we can ascertain which individuals inherited the genes conferring vulnerability to alcohol and who did not. Extensive diagnostic instruments were created for this project, hundreds of subjects and families have been interviewed, a complex computerized pedigree database has been incorporated, and all the techniques of statistical genetics and molecular biology are being applied to "informative" families. Data from nearly three thousand individuals have been collected. Genotyping of the entire genome for genetic markers linked with alcoholism is nearly completed and linkage analyses are underway with results expected within the next two years. Our intramural program is also participating in this activity. In addition, COGA's standard interview procedure has been translated into several languages and is now in use internationally.

Additional efforts to understand the genetics of alcoholism include sophisticated quantitative trait loci (QTL) mapping studies. QTL mapping has enabled researchers to identify specific alcohol-related genes in mice and is expected to provide clues on the location of corresponding genes in humans. In FY 1997, NIAAA plans to initiate additional research to precisely map the location of the genes, isolate them, and identify their protein products. Also in the upcoming year, investigators will begin to apply a complementary approach to QTL mapping that uses chemicals to artificially induce mutations in mice to identify alcohol-related behavioral traits. This approach is an efficient, direct method for discovering the genes that determine vulnerability to alcohol.

There are four major payoffs expected from this line of research: 1) Identifying the genes and their products will lead to the design of better pharmacotherapies; 2) Increased knowledge of vulnerability will define who is at risk so that those most in need can be targeted for appropriate interventions; 3) Precision in genetic understanding will allow us to clearly define the role of the environment in increasing the risk for alcoholism; and 4) Increased definition of normal physiology will result from studying the abnormal.

Alcohol use affects not only the functioning of the brain, but other major body organs, as well. Organ damage is the major medical consequence of chronic alcohol abuse. This damage is primarily on the liver, brain, cardiovascular system, and pancreas. A recent NIAAA-sponsored study demonstrates that treatment with the antibiotics polymyxin B and neomycin, which target intestinal bacteria, prevented alcohol-induced liver injury in the rat model. This approach provides a potential new strategy for preventing and managing alcohol-related liver disease. Research in these areas is very promising and the potential medical payoff is in the prevention of cirrhosis. Also, the coronary protective effect of moderate alcohol use, its mechanisms of protection, as well

as the risk-benefit tradeoffs of moderate drinking at different stages of life are being investigated.

The NIAAA continues to pursue the development of medications to treat alcohol dependency and its medical consequences. Understanding the biological bases for alcoholism and the phenomenon of craving may provide new pharmacotherapeutic possibilities. And, the development of new medications to prevent relapse to alcoholic drinking will have a major impact on the effectiveness and cost of health care in the treatment of alcoholism.

Naltrexone, as the committee is aware, is the first drug approved for the treatment of alcoholism in 40 years. The discovery of the usefulness of naltrexone for alcoholism treatment is a direct result of NIAAA-sponsored research inspired by both clinical observation and neuroscience. Naltrexone acts by blocking opiate receptor cells in the brain. Naltrexone, in combination with counseling, has two main effects: it lengthens sobriety and in cases where a patient does experiment with alcohol, naltrexone reduces the number of "slips" that become full relapses. Ten NIAAA-sponsored clinical trials are now determining which groups of patients are most responsive to this medication. The benefits and side effects of long-term use of naltrexone are also under investigation. In addition, clinical trials that incorporate psychosocial treatment elements in conjunction with naltrexone are promising to yield better information about which populations will most benefit from this medication.

Acamprosate, a European compound that acts on specific brain receptors, is being tested in clinical studies throughout Europe with promising results. Upon its approval for investigation in the United States, NIAAA will participate in developing clinical trials with acamprosate. A variety of other medications are also being tested throughout the United States in well-designed clinical trials. Our intramural program is heavily involved in such clinical research, and the construction of the new clinical center will enable us to better conduct our clinical research. The configuration of the new facility with its larger outpatient capacity and smaller inpatient hospital will allow us to serve our investigators' interests more effectively. The associated essential clinical laboratories will be in proximity to the patient areas, enabling us to utilize available resources more efficiently. For example, we will be better able to effectively control the amount of care provided to patients during the weeks they participate in our research.

Fetal Alcohol Syndrome (FAS) continues to be a priority at NIAAA. FAS is one of four leading known causes of mental impairment in the United States, affecting between 1 to 3 infants per 1000 births. However, FAS is the only birth defect in this group that is completely preventable. FAS is costly to treat -- 1992 estimates indicate the direct cost of FAS to be approximately \$1.9 billion.

The NIAAA continues to disseminate the message that FAS is entirely preventable. An NIAAA-supported randomized clinical trial will measure the effectiveness of reducing FAS by combining generalized health education messages on alcohol and pregnancy with specific, individual-focused interventions for pregnant women using alcohol. The NIAAA has made it a priority to target communities that are

not being reached by educational efforts. The NIAAA released a new program announcement, *Intervention Research to Prevent Alcohol-Related Problems*, to stimulate the design, development, and/or testing of interventions that have the potential to prevent Fetal Alcohol Syndrome and other alcohol-related problems. We have also initiated an NIH-wide interest group involving five other institutes that focuses on the teratology of alcohol to improve communication and collaboration on FAS and FAS-related research. Although much progress has been made in elucidating the underlying mechanisms of FAS and in characterizing fetal outcomes, NIAAA remains committed to furthering the understanding of the effects of alcohol on fetuses and children as reflected in the recently completed National Academy of Sciences, Institute of Medicine study of FAS. And, finally, I am pleased to announce that the judges of the 1995 International Blue Pencil Competition of the National Association of Government Communicators awarded *Alcohol Health & Research World: Alcohol-Related Birth Defects*, first place in its category of technical publications.

In addition to our basic science and clinical portfolio, NIAAA maintains an active research agenda in prevention and health services research. The goal of NIAAA-sponsored prevention research is to obtain scientifically objective and measurable effects attributable to specific interventions. To ensure the acquisition of meaningful results that are generalizable to other locations, these studies employ rigorously defined scientific methodologies including random selection and control communities. In addition to providing effective prevention interventions, this type of research also contributes to the discourse on public policy. The NIAAA research has contributed scientifically derived data to the public debate concerning raising the legal drinking age which has saved lives. Furthermore, the positive effects endure past the age of 21. Other NIAAA-funded studies provided the data to show that lowering the legal blood alcohol limit for young drivers reduced fatal single vehicle night-time crashes (the type of crash most likely to involve alcohol) among adolescents and that the lower the limit is set, the greater the reduction. The NIAAA is using its health services research resources to conduct studies on managed care and alcoholics in treatment. The goal of NIAAA-sponsored health services research is to develop a knowledge base which can be used to improve the efficiency and effectiveness of services for alcohol-related problems. Alcohol health services research seeks to evaluate both treatment and prevention services in applied settings. Multidisciplinary in scope, the NIAAA program funds studies on the impact of organization, financing, management and delivery of alcohol-related health services on service accessibility, quality, utilization, cost, and outcome. Included in this spectrum is research that focuses on identifying factors that influence the effectiveness of health services delivered to heterogeneous groups of subjects in "real world" clinical and community settings and the effects of managed care on the delivery of treatment for alcoholism.

In conclusion, we are making genuine progress in advancing our understanding of the complex nature of the effects of alcohol on the human mind and body. The future holds great promise for the development of effective prevention and treatment strategies. Thank you.

Mr. Chairman, the FY 1997 budget request for the NIAAA is \$192.3 million. I would be pleased to answer any questions you may have regarding this request.

Enoch Gordis, M.D.
Director
National Institute on Alcohol Abuse and Alcoholism

Enoch Gordis, M.D., became the Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in October 1986. Prior to this, he was Professor of Clinical Medicine at Mt. Sinai School of Medicine, New York City, and a staff member of the Elmhurst Hospital in Elmhurst, N.Y., where he founded and directed the hospital's alcoholism program from 1971 until his appointment to NIAAA. This large comprehensive program, with both inpatient and outpatient components, served some 15,000 patients during his tenure.

The NIAAA, a part of the U.S. Department of Health and Human Services' (HHS) National Institutes of Health (NIH), is the principal Federal agency for research on the causes, consequences, treatment, and prevention, of alcohol-related problems. Through an intramural scientific program, which includes a 14-bed clinical research facility on the National Institutes of Health (NIH) Bethesda, Maryland Campus, and through an extensive array of extramural research grants and contracts, NIAAA supports studies in a variety of biological and behavioral areas such as, neurosciences, pharmacology, epidemiology, genetics, molecular biology, and prevention and treatment. The Institute also supports research training and health professions development programs, and research on alcohol-related public policies that provide HHS and other Federal, State, and local government decisionmakers with state-of-the-art analyses of the relationships between public policies and alcohol-related problems. The current NIAAA budget is \$198.6 million.

Dr. Gordis trained in internal medicine at the Mount Sinai Hospital in New York. During this period, he also was a research fellow in Dr. Solomon Berson's laboratory at the Bronx Veterans Administration hospital. Following his residency, Dr. Gordis spent 10 years at New York City's Rockefeller University in the laboratory of Dr. Vincent Dole, conducting research in the areas of lipid metabolism, toxicology of carbon tetrachloride, analytical biochemistry of drug stereoisomers, the metabolism of alcohol and alcohol withdrawal. He has published on the clinical evaluation of alcoholism treatment, biological markers of drinking, disulfiram therapy, and the relationship between science and social policy.

As NIAAA Director, Dr. Gordis' principal goal is to continue support for activities designed to give maximum visibility to the Institute's role as a leader in alcohol-related research and the integral part of that role in preventing and treating alcohol abuse and alcoholism. This will include continued support for NIAAA's extramural and intramural research programs; support for a continuing Institute role in health professional education; increased attention to public policy research; and enhanced data collection and dissemination activities.

A member of Phi Beta Kappa, Dr. Gordis received his B.A. degree from Columbia University in 1950 and M.D. degree from the Columbia College of Physicians and

Surgeons in 1954. He is a member of the Institute of Medicine of the National Academy of Sciences, the American Physiological Society, the American Federation for Clinical Research, Sigma Xi, the American Gastroenterological Association, the American Society of Addiction Medicine, the Research Society on Alcoholism, and Fellow of the American College of Physicians.

INSTITUTE COORDINATION

Mr. PORTER. Thank you, Doctor. Let me thank all of our witnesses on this panel.

My first reaction to our experiment, Dr. Varmus, is that it may work fine if there is one person up here, but what if there are 13 and all have questions? I wonder whether we can get through it all.

But since we are in this mode, which I think is fortuitous since the House is not in session today, I think we can cover fairly well all the ground we want to cover.

Dr. Varmus, I think the first question is for you. You have four institutes that, in some sense, may overlap one another. How do you determine when there is something going on in one that might also be going on in another—in other words, how do you avoid duplication, and how do you work with one another to address that kind of problem and the jurisdictional problem, which institute does what?

Dr. VARMUS. One of the ways this is done is through the referral process that assigns grants to different Institutes. That is the means by which any individual application becomes assigned to one institute.

Frequently when grants are at the boundaries between institutes, the institutes will consult with the referral process to be sure which direction things should be moved in. That is an ad hoc mechanism.

In answer to your question, more important are the coordinating activities that have emerged over the last few years to try to sort out the kind of problems you are anticipating.

For example, there are at least four institutes, perhaps more, that have a role in Alzheimer's disease. Certainly the Neurology Institute, Dr. Hyman's institute—NIMH, the National Institute on Aging, the Nursing Institute, are among the major players in that area. Those institutes have been working very actively through a coordinating group. The institute directors frequently get together to look at their portfolios to fund things together, if necessary; or to make assignments to one another depending upon the emphasis and the grant. We try to do this with several diseases that are addressed by multiple institutes.

Although all the institutes assembled here address a single organ, they are looking at different diseases or at the social effects and medical effects of different kinds of drugs of abuse; in the vast majority of cases it is not difficult to make assignments of grant applications to one institute or the other.

When there is potential for overlap, the emphasis has been on coordination among program staff, directors, and the Division of Research Grants referral process to make sure that there aren't undue overlaps.

Mr. PORTER. Since all four are before us, why do we need an institute on substance abuse and an institute on alcoholism and alcohol abuse separate from one another? Aren't they both drugs? Although one is legal and the other is illegal, aren't they both drugs, and why do we have to have separate institutes?

Dr. VARMUS. I would make the argument that the kind of drugs at issue are, in a disciplinary way, rather different. Certainly the

kinds of questions that are being asked have some commonality but many more differences.

With respect to the mechanism of action and the effects of alcohol on many organ systems, I find it very easy in my own mind to make the divisions. If we had one institute that dealt with all of these, I don't see that as an impossible situation, but it is certainly working extremely well under the current circumstances.

We don't mean, in having several institutes working on the brain, to say that once a grant has gone to one institute it is only that institute that pays attention to what comes of it. We fully expect that Dr. Hyman and colleagues will profit from research done in Dr. Hall's institute and vice versa.

The actual expenditures are divided along what we believe to be disciplinary lines, but it is frequently difficult to know exactly where the benefits for one disease will come from, especially when we are all dealing with the same organ. It is fully anticipated that the consequences of research in one institute will have dividends for many of those who are working on the various diseases.

ESTABLISHMENT OF NIAAA

Mr. PORTER. My question is not meant to convey hostility to either NIAAA or NIDA but merely to ask the question, and I assume there is some historical context here where alcohol was perceived as being a problem first and drugs came along perhaps later. Can you share that with us?

Dr. VARMUS. I don't know the history.

Dr. GORDIS. The history is that, due largely to the efforts of then Senator Harold R. Hughes, the Congress created NIAAA in 1971. In fact, this is our 25th anniversary year, which is coming to its conclusion in Washington in June. That was the only time that Bill Wilson, the founder of Alcoholics Anonymous, stepped out of his anonymity to testify. NIAAA's establishment had a lot of support. President Nixon signed the measure close to the waning hours of the year when time was just about to run out. NIDA was founded a year or two later, also, I think, through the ministrations of Senator Hughes.

But I must say that had it not been for the support of recovered alcoholic constituents, including several major leaders of industry, plus the support of certain members of government, and the fact that Bill Wilson from AA came out strongly, it probably would not have been our institute, and certainly not NIDA, which followed a couple of years later.

That is the history.

I would also be happy to comment on the question you asked Dr. Varmus before.

There are commonalities between certain of the neurocircuits involving reward for drug use, between alcohol and drugs. As far as the institutes go, I feel strongly that they should be independent, but I understand the counterargument which has been said many times. However, the fact of the matter is that in many respects we have a very different domain of concerns, constituencies, and research.

First of all, alcohol is a legal substance. That means all the research having to do with prevention, regulation, economics, and so on is vastly different than that having to do with illicit drug use.

Second, alcohol by far, has a wider range of organ toxicity than illegal drugs. Liver disease itself causes 12,000 deaths a year. Alcohol damages the heart. It also has protective effects. Alcohol damages the brain, not only as far as addiction, but causing permanent dementia. It is the second leading cause of dementia in the country after Alzheimer's.

So we have a range of organ toxicity, which I think is far different, and therefore one might say that we have interests in collaboration with other institutes on liver disease, with Aging, on alcohol and aging and so on.

So for these reasons the historical development of the institutes, I think, has a justification in both the nature of the research as well as in legislative history. It is working fine. We collaborate on things where collaboration should be happening, but, on the other hand, there are certain domains which are radically different.

Mr. PORTER. I assume that any other drug other than alcohol goes under Dr. Leshner's jurisdiction. If it is caffeine, that is a drug.

Would that be under your jurisdiction?

Dr. LESHNER. Yes, sir. We do do some caffeine research, but really very little. We also do nicotine and marijuana research.

IMAGING AND ALCOHOL

Mr. PORTER. Dr. Gordis, have you done the same kind of thing as Dr. Leshner has done with the effects of alcohol and imaging?

Dr. GORDIS. Yes.

In the interest of time, I couldn't select one area of neuroscience for highlighting, but we have very dramatic things going on as well. We are using PET scanning, MRI, and, functional MRI, to look at several different things: What happens to the brain during withdrawal? Which parts of the brain are attacked by alcohol? We have work which indicates that using benzodiazepines, which are a group of drugs like Valium, which have parallels with alcohol, for example, they relieve each other's withdrawal symptoms and cross tolerance develops to them—showing that sensitivity to benzodiazepines differs in alcoholics even before they have been drinking in some cases.

We have extensive imaging research on the damage alcohol does.

Mr. PORTER. I am anxious to know, do you share the approaches or processes with one another so, if you do something that looks promising, would you call Dr. Varmus and say—

Dr. GORDIS. There are a variety of routes of communication. As you know, Dr. Varmus has strongly encouraged trans-NIH interest groups. We often go to the same neuroscience meetings, talk to each other; and some of our researchers have grants from more than one institute. I don't think that the communication of the application of technology itself is a problem at all.

Mr. PORTER. Maybe what we need to do is to get Congress to work this closely together with one another.

Dr. VARMUS. We have a one-party system at the NIH.

Mr. PORTER. My staff has prepared questions for each of you, most of which, I am afraid, we probably won't be able to get to.

Dr. Hyman, you have been on the job less than a month.

Dr. HYMAN. One week.

NIMH PRIORITIES

Mr. PORTER. One week.

NIMH has been without a permanent director for almost 2 years, and I assume that many things have been put on hold pending your appointment. Have you identified the top two or three issues that you believe need your attention first at NIMH?

Dr. HYMAN. Yes, I have.

Although Dr. Cowdry has done a remarkable job not only as acting director but also in the transition, there are a number of really pressing needs of which the first and foremost is the revitalization of our intramural research program.

Our intramural program is a substantial intramural program which accounts for approximately 15 percent of the NIMH budget. The intramural program contains some of the best known and most talented scientists in the arena of mental health, but it is also in some need of renewal, not because the investigators themselves have slipped, but rather because we have a cohort of people who have been very successful as a team, and, as a result, it has been very difficult to recruit new people in. Other younger individuals who have matured within the system and who are now vigorous midlevel scientists, have inadequate resources.

Prior to my arrival, Drs. Varmus and Cowdry put together a blue ribbon panel of scientists to examine the intramural program. I look forward to their report by January, which will be aimed at revitalizing the intramural program. I look forward to their breaking down rigid structures that have grown, for historical reason, not scientific reasons, and providing a revitalization which will return this currently outstanding program to its jewel-like status which it exhibited in previous years.

A second important priority is that, as you know, the former Alcohol, Drug Abuse and Mental Health Administration Institutes rejoined the NIH, and, in the authorization process, there was a suggestion that is endorsed by the NIH of having our review programs rejoin the NIH mainstream. This is both a concern and an opportunity.

The existing NIH study sections or review groups work extremely hard and could not tolerate an influx of an extra 80 or 90 grants from my institute or from NIDA or NIAAA, and on the one hand, we have this administrative issue to handle. On the other hand, however, it is a real opportunity. When you change review, one can look at potential guild-like effects that can occur over time and sort of open a clearing where the best cutting edge science can occur.

This is going to be a process that is going to require a great deal of thought and negotiation, but I see it as a real opportunity to revitalize what is already, I think, very good science.

I could go on, but unless you want additional priorities, these are two of the most pressing.

I must add, though, that these are administrative priorities. We also have some important scientific priorities that I won't take very

long on. One would be to develop a tradition in psychiatry of what we might call translational research; that is, greater communication between basic bench scientists and people doing clinical research that will increase the speeds with which we can exploit the kinds of discoveries that are being made with molecular and cellular approaches in the service of understanding and treating illness.

Mr. PORTER. You have actually answered several of my questions all at once.

You have been quoted as saying there is too much incremental research being conducted at the NIMH intramural program. Does this imply that you think the role of the intramural program should be to conduct research that can't be done anywhere else in the extramural community?

Dr. HYMAN. Those are the kinds of remarks that got me sentenced to a bit of media training before I started my job.

What I meant, which I think is true, is that the intramural program has the remarkable advantage, in some sense, of review after research has been done, whereas those living in the extramural program have to justify their future research.

The dangers of justifying your future research are too much conservatism and not enough risk taking, because study sections, especially in times of financial constraints, get conservative. They are looking for reasons something might not work. So I am hoping for, in the revitalization of the intramural program, an appreciation for taking sensible risks.

What I mean by incremental research is not bad research but research which does the next obvious experiment, instead of saying, given what we know, what would have the greatest payoff even if there is some risk that it might not work? I would like to instill that spirit in the intramural program.

NEURODEGENERATIVE DISORDERS

Mr. PORTER. I have Members of Congress I would like to send to your media training seminar.

Thank you, Dr. Hyman.

Dr. Hall, Dr. Varmus intends to use his 1 percent transfer authority to begin a neurological disorders initiative with several institutes participating and your institute coordinating. Can you describe the planned initiative and explain how this will differ from efforts the institutes make independently? Are there any particular diseases targeted in this initiative? And how does this effort relate to the neurodegenerative disorders initiative that was encouraged in the Senate report last year?

Dr. HALL. First of all, let me begin by saying that this is, as we all believe, a time of unusual opportunity in brain research, and, to echo Dr. Hyman's comments, it is a time when the interchange between basic science and clinical medicine has never been more fruitful. As a colleague said, medicine has never been more biologically interesting than it is right now. And there is the sense that not only does biology have a lot to contribute to clinical medicine but also the reverse.

We wish to facilitate research at the interface and to bring to bear the remarkable advances that have occurred in fundamental neurosciences on problems of disease.

There are several areas that deserve particular emphasis. One is in the area that you mentioned. That is the neurodegenerative diseases. There are a number of diseases including Alzheimer's disease, ALS, Lou Gehrig's disease, Huntington's disease, and Parkinson's disease, in which a specific group of nerve cells dies for reasons that we do not know. There have been suspicions in some cases that they are environmental reasons; there may be genetic predispositions; there may be complex interaction. But in actual fact, in none of those cases do we know why particular cells die.

What we have learned recently is that there seems to be a common body of knowledge about how cells respond to injury and about how cells live and die, if you will, that is relevant not only to these diseases but also to diseases such as stroke, to brain and spinal cord injury, and in fact to any disease in which nerve cells are stressed or put at risk, and we believe that one source of the problem is what is called oxidative damage—that is, the very reactive species that arise in the cells because of metabolic reactions that create damage that must be repaired in some cases.

And there is an interesting interplay between these oxidative mechanisms and what we might call a group of pathways that control the life and death of nerve cells. They have found through work in very simple organisms, worms being the primary example, that cells appear to have pathways by which they commit suicide, literally. These pathways are used in development. We produce many more nerve cells than we need. Some then are pared away to create the nervous system that emerges during development.

We think the same mechanisms may also be at play as cells respond to injury, so that if cells become injured too badly or if they receive certain signals, they activate these pathways and they commit suicide.

These pathways are under close regulation. We know that there are proteins which suppress these pathways and there are others which activate them. We are busy learning more about these.

This is one of the areas of emphasis that will emerge, I think, in the initiative and one that is particularly relevant for neurodegenerative diseases. If we can understand it, we understand these pathways. Then in relevant circumstances we can act to try to suppress the death pathways, if you will, or to encourage those proteins that normally suppress them and to try to encourage the cells to rescue themselves from damage.

Another active area that you have heard about is genetics. This is relevant for alcoholism, for drug abuse, for neurological disease, for psychiatric disease. This is an incredibly powerful tool that our generation has in the sense of being able to find genes that are responsible for particular genetic diseases.

As we get more and more sophisticated, we realize that there are not only genes that are directly responsible for disease but genes that interact in more subtle ways so that they predispose to diseases. We look forward to trying to fish those out.

One area is with respect to Parkinson's disease. Our institute, along with the Aging Institute, Mental Health Institute, and Envi-

ronmental Health Sciences, had a conference last summer on Parkinson's disease. I received this week the report from that conference, delayed a bit because of the furlough, but finally here.

One of the conclusions that we came to was that the contribution of genetics to Parkinson's disease was perhaps more than one had realized. As a result of that, we plan a program announcement this year and have already, within a month of the conference, contacted a group with a large family containing many members with Parkinson's disease, and put them in touch with a group at the Human Genome Center, working with the latest techniques in molecular genetics. We hope within a matter of months we will have some indication of whether genetics is at work here and, if so, to try to locate it.

COMPLEX GENETIC TRAITS

Mr. PORTER. I seem to be hearing more recently about the involvement of multiple genes and complex interactions among them than I did previously. Is this something that has been recently found as a result of genetic research? Did people in the scientific community originally think it might be more simple and easy and it has become actually quite complex even though we can map the entire genome system?

Dr. HALL. The progress of science is to start with simple things and then to progress to more complex situations. One starts with a case like Huntington's disease, where there is a very clear relationship, for example, between a defective gene and whether or not you get the disease. If everybody who has a defective gene gets the disease, the genetic problem is not so difficult in terms of sorting it out.

The initial progress occurred with diseases like cystic fibrosis, Huntington's disease, muscular dystrophy. For the nervous system more than 50 different genes have been identified that contribute in a rather direct way to disease. As genetic methods become more sophisticated, it has become possible to fish out, if you will, more and more subtle influences.

Now this requires a large enough sample—and the other factor in this is that it requires a very large volume of work. So as techniques have become more automated, it has been possible to do this. One can pick out as much as a twofold difference in the incidence of a disease. That is, that the gene may contribute increased susceptibility by as little as twofold and still be detected under favorable circumstances.

I think for things like epilepsy or stroke, which you wouldn't initially characterize as a genetic disease, we will be able to tease out more and more effectively the various contributing strands that predispose or in some cases protect.

NEW THERAPY FOR STROKE

Mr. PORTER. You talked about progress on stroke and the clot buster drug. If stroke is not usually treated as an acute emergency event, how did the clinical trials testing the clot buster drug find enough patients to try it out on?

Dr. HALL. That is a very good question. We had 18 centers, and these represented a variety of medical settings ranging from urban

hospitals to university hospitals to small community hospitals. At each one of these, a rather intensive effort was required, in some cases involving more than a thousand people at a single site in order to educate the whole community about this.

That is, to treat stroke as an emergency requires, first of all, the patients and their physicians to be alerted that when symptoms are detected the wrong thing to do is to say let's wait and see how we feel in the morning. The right thing to do is to get immediately to a hospital. Paramedics must realize this is an emergency, see that people are brought in promptly. The hospitals have to be reorganized in ways that one might not relies.

Some strokes are thrombotic, caused because something clogs up an artery, and other strokes are hemorrhagic, caused because a blood vessel breaks. The worst thing would be to give a clot buster like CPA to somebody who had a hemorrhagic stroke. So first you have to determine is this stroke is thrombotic or hemorrhagic. That is done through imaging.

In order to get the patient treated within 3 hours, hospitals have to have procedures where emergency stroke patients have priority on imaging machines, bump anyone else in line, get a quick read, and sometimes it is a two-step process where you first, determine the cause and then locate the clot. So the whole community has to be geared up to do this.

An encouraging thing about this study and one of the things we are proud of about it, is that our institute played a very important role paving the way for this study over the last 10 years and then in organizing it. One of the most important things is that we now have a model in different settings for how to do this. So we know that people have strokes all over the country. You don't have to get to a major medical center in order to get this effective treatment. There are models of how to do this in even modest hospitals. What is required are imaging machines and education.

COCAINE ADDICTION RESEARCH

Mr. PORTER. Thank you.

Dr. Leshner, you have made treatments for cocaine addiction your institute's top priority. If we can believe press reports, methamphetamine, or crank, will be the next drug menace. Will the results of your research on cocaine be transmittable to other drug problems like crank, or will you have to reinvent the wheel?

Dr. LESHNER. Let me clarify by saying something about methamphetamine. We are seeing an alarming rise in methamphetamine use, particularly in the Southwest and on the West Coast. But, I am concerned that we not spread too much concern or attention to the issue prematurely.

Having said that, we have learned quite a bit about Methamphetamine. Because of the commonality of its effects and those of cocaine—both are stimulants—research on cocaine is instructive. In our research on addiction with cocaine, we are looking not only specifically towards cocaine, but also to those mechanisms that either all addictions share in common or those mechanisms through which cocaine and methamphetamine work similarly.

For example, on aspects of dopamine neurotransmission there would be commonality in the benefits. That is, we believe that

there is a common brain mechanism underlying all of addiction, and therefore a medication directed at that of course would benefit methamphetamine as well. Methamphetamine and cocaine have some mechanisms of action in common and some that are different.

Mr. PORTER. In your testimony you indicate that researchers have successfully immunized rats against the stimulative properties of cocaine. Does this imply that some day we may have a vaccination against cocaine addiction?

Dr. LESHNER. Obviously, moving into the vaccination of humans against cocaine is a difficult and complex issue on many levels, scientifically and medically. And there are a variety of social issues that have to be addressed.

What the data have shown so far that I think is important is that we are able to prevent cocaine's passage into the brain through an immunization process. When you do that, you then decrease cocaine's stimulatory effects.

We are at a very early stage. We have begun discussions with a large number of groups around the ethical and social issues concerned with the question of immunization or vaccination of humans.

Technically, I believe it is highly likely we would be able to do it based on the data we have so far, and there are a variety of approaches that might be taken.

Mr. PORTER. Do we have an indication whether this vaccine would work only on cocaine, or would it work on other drugs as well?

Dr. LESHNER. This particular vaccine is for cocaine. It causes the production of antibodies to cocaine itself, and therefore this is directed at cocaine.

MANAGED CARE

Mr. PORTER. Dr. Gordis, has the move away from the standard 30-day residential treatment protocol for substance abusers forced by managed care had the side benefit of encouraging lower costs and more varied, individualized treatments for patients?

Dr. GORDIS. That is a complex question, Mr. Porter. It depends on our knowing some things which, in part, we don't know yet.

For example, there is no question that the role of research in supporting assertions about the effectiveness of treatment is of relatively recent history compared to the tradition of long-term residential treatment for alcoholism as well as other drug abuse.

One of the things we are very proud of is that all our treatment research, whether it is verbal treatment or issues of rehabilitation or detoxification, is based on the soundest possible experimental design of clinical trials. That is a relatively recent arrival in the history of treatment.

Therefore, it is difficult to know exactly what baseline success rates were for unresearched rehabilitation units in the past. So that is the first area of doubt. We don't have the firm baseline on which to make the comparison.

Clearly, it is cheaper if you don't do it. The question, however is, is the final payoff cheaper? That is, by saving money at the outset for certain inpatient or long-term rehabilitation, are you therefore going to simply make the treatment more effective and cheaper, or

are certain people being deprived of treatment which would give them a much better shot at long-term sobriety and the avoidance of the very expensive complications of alcoholism? The answer right now is, we don't know.

Much has to do with the whole managed care issue to which several of my colleagues have alluded. We have a research announcement on managed care, already have several grants on this, and are expecting to fund quite a few more during the next year. Because the issue of managed care is what is driving the whole issue that you raised in your question. That is, when the issue of cost saving is driving certain decision-making, is it simply making treatment more efficient or are patients being deprived of access and the best therapy possible?

Most of the evidence we have on this is largely anecdotal. For that reason, I think that health services research, especially on the managed care issue, is of paramount importance.

Mr. PORTER. What kind of interface do you have with the Agency for Health Care Policy and Research on these kinds of questions, if any?

Dr. GORDIS. We have a portfolio of research specifically geared to alcohol. They have certain databases in which we participate. We also have worked with them in several combined conferences to plan out our research.

Mr. PORTER. Isn't that kind of thing something that they ought to take the lead on and you ought to provide the data and the research on?

Dr. GORDIS. That, too, is a complex question.

But let me say that there is a great advantage when the people who know the intricate details of the clinical problem are the ones who are studying the issue of the care. Because the issue of the financing of care and the economics of care are not divorced from either the research or the clinical experience of people who have devoted their whole professional lives to solving problems associated with alcohol abuse and alcoholism. So I would say in general that the roles that are being served now are probably rational.

EFFECTS OF MODERATE DRINKING

Mr. PORTER. I think this is going to take our attention for some time to come as we see more than anecdotal evidence coming out of the actual treatment.

A study published last summer in the *Journal of the American Medical Association*, found that heavy drinkers are more at risk for developing the irreversible heart disease cardiomyopathy and that women drinkers are more at risk than men. Has this effect of heavy drinking on the heart been established for some time and how does it mesh with the findings that moderate drinking protects against coronary disease?

Dr. GORDIS. Alcoholic cardiomyopathy is a syndrome which has been well-recognized for decades. The mechanism by which heavy drinking causes damage to the heart muscle is being looked at by researchers and has been, especially in the past 6 or 7 years, with all the tools of modern cellular biology.

It is a very serious issue because heavy drinking leads to a condition where the heart muscle becomes inefficient, flabby, and di-

lated, leading to arrhythmias, dilation of the heart, and chronic heart failure from which many do not recover, although prolonged abstinence in some cases can reverse it either in whole or in part.

What is novel about the report you are referring to is that this is another example where women seem to be especially vulnerable. This is not a new observation in the toxicology of alcohol because it has been known for quite a few years that for a variety of reasons, including perhaps the difference in distribution of body mass, women with a shorter history of drinking and perhaps at lower doses are more susceptible to alcoholic liver disease. This is a gender difference in the toxicology of alcohol, and I don't think we know what it is due to, but it will be a source of research questioning.

Mr. PORTER. How can moderate drinking protect and heavy drinking damage? What is the mechanism for moderate drinking protection against cardiovascular disease?

Dr. GORDIS. This issue is the subject of our recent Request For Applications on the topic to which we have a tremendous response, 62 applications will be reviewed shortly. For a while, there was controversy over whether moderate drinking, which we will say for sake of our definition, means no more than two drinks a day for men, one for women and for the elderly, really is protective or whether some of the data were an artifact because people who didn't drink at all, could really have been "safer" than those who drank one or two drinks a day.

However, I think the epidemiologic evidence is now overwhelming that moderate drinking—maybe not at the level of one or two drinks a day, for the evidence now is tending to show that one drink every couple of days can probably achieve the same effect—has coronary protective effects measured either by heart attacks or by coronary deaths and also by total mortalities, since coronary deaths are such a large factor in total mortalities.

The mechanisms really lie along three main lines and they are being investigated because their relative role is not certain in all classes of patients. The first is that alcohol modifies the pattern of lipoproteins, those fat-carrying proteins in the blood which have their own designation, some of which are known to be risk factors for heart attacks, others which are known to be protective. Alcohol is known to raise high density lipoproteins or HDL.

On a more acute basis, alcohol is known to interfere with certain aspects of blood coagulation, the immediate event before coronary thrombosis. This especially involves platelet aggregation, which is one of the first steps in blood clotting, and a few other more complex mechanisms which I won't go into now.

Finally, there is some evidence that some of the components found in alcoholic beverages known as antioxidants may have some role in slowing down the atherogenic process. This is a matter of research questioning because not all of the antioxidants are absorbed from the intestinal tract after drinking in a dose sufficient to mimic what you see in a laboratory test tube.

These are the three main routes by which we are looking at the mechanisms of the protection of moderate drinking. But the problem with the topic is that as soon as you escape from these low levels of drinking, you begin to increase the risk for fetal alcohol ef-

fects, for hypertension, for driving accidents, et cetera. So a main issue in our research is not only a description of the mechanisms that probably protect the heart, but what are the trade-offs of risk/benefit analyses for different stages in life and for different sub-populations.

EFFECTS OF MODERATE DRINKING

Mr. PORTER. The difficulty is that the consuming public gets a hint that there may be some benefits here and that provides a rationale for probably more than moderate drinking and creates some of the other problems that you have to face.

Dr. GORDIS. I agree. I think the distinction that is implied by your remarks is the difference between what an individual doctor says to his or her patients versus what rational social policy ought to be, and they are not the same thing.

BEHAVIORAL RESEARCH

Mr. PORTER. Dr. Hyman, through the years the subcommittee has heard from outside groups about behavioral research, both those who think NIMH should support more work in this area and those who question its role in a biomedical research institute. Could you lay out your vision of the role of behavioral research at NIMH?

Dr. HYMAN. That is indeed a contentious question. Part of it is that the term behavioral research covers an immense waterfront, sometimes extending from research that could go on and does go on in basic neuroscience labs studying the behavioral aspects of animals, to kinds of research which are very far removed from the brain and from individual patients. The real question for the NIMH research portfolio is not should we be doing behavioral research—of course we must, because in the end, the diseases that we are worried about manifest as behavior—but rather where should the edges of the portfolio be?

First, let me talk about some of the opportunities in behavioral research, I want to highlight two things. The first is that we are now able to manipulate the mouse genome pretty much at will. One of the most exciting outcomes of being able to change genes in the mouse is that it helps us understand what the molecular genetic research we are doing actually portends for the functions of the brain; that is, to see alterations in the behavior of these experimental animals and then to relate that to the circuits in the brain and functioning of the cells.

It has become clear that many of the most outstanding labs that do genetics and neurobiology now need, in essence, either a crash course in behavioral research or a collaboration with behavioral scientists. Both in animals and in humans I see molecular genetics as creating what should become a golden age of behavioral research because one will have markers of vulnerability, one can ask what are these genes doing in the brain. We now can begin to examine, perhaps in vulnerable human beings, assuming we are very, very careful about protecting their confidentiality, specific risk factors for mental illness. We are beginning to understand the whole gamut of risk factors which might range from perinatal infection to life experience.

A second area is illustrated in these very interesting brain images from Dr. Leshner. Indeed, neuroimaging, which allows us to see the thinking, feeling, living human brain is becoming absolutely the dreamt-of bridge tool that now enables us to move between animal research and human research. But we have to use it well.

In the flush of enthusiasm for neuroimaging, we are beginning to realize that the way to utilize these very expensive tools well will be to rely not only on a knowledge of the circuitry of the brain provided by neuroscientists, but also on the tradition of psychology out of which cognitive neuroscience and computational neuroscience are going to help us design activation tasks for patients so we get something meaningful when they are being scanned.

When somebody goes into a "tube," perhaps you think you are studying obsessive-compulsive disorder but actually the patient is worrying about how claustrophobic it is in the tube. Somebody else might have their mind wandering, thinking about a television program. So we need to utilize the techniques of behavioral science to ensure that these hard-won results are meaningful, and when you talk about the memory of drugs, that is behavioral research.

As far as what should be the boundaries, how far away from the brain should we get, I think that well-meaning, honest people can disagree. I intend to learn much more about the NIMH portfolio. I know we have just had a Task Force study and a book published on basic behavioral research. Now, I want to consult with the people who were involved with the study, if necessary convene a group of thoughtful advisors, work with Norman Anderson, who is thinking about the role of behavioral research in each institute, and try to come up with some really rational ideas so that we are funding the kind of behavioral research that is going to inform our core mission.

I want to add, I think it is important that Dr. Varmus has brought Dr. Anderson on board, because it is very important to recognize that every disease has behavioral aspects and it wouldn't make any sense to be studying the behavioral aspects of cardiovascular disease in the National Institute of Mental Health. It is really much better done in the Heart Institute, and of course aside from picking your parents, the most important aspects of determining whether or not you are going to get heart disease are behavioral.

Mr. PORTER. Are you prepared to defend all of NIMH's grants to Sam Donaldson?

Dr. HYMAN. I have two answers to that. The first is this is one of the advantages of being new. I can tell you with honesty that I have not read the entire portfolio but I will look into it. But I hope that I would not find much to be embarrassed about, and indeed I look forward to working with the staff to make sure that all of our portfolio is very much on target.

The issue you are referring to was raised not with respect to behavioral research, but actually some aspects of our basic portfolio were attacked, for example, the study of songbirds and roundworms. It turns out that it is easy to take isolated pieces of a puzzle and not see where they fit in. But the songbird is the best

example of a higher order animal that is constantly rebuilding its brain and rewiring it properly.

For example, not only with respect to things like paralysis where rewiring is critical, but if schizophrenia is, as is likely, a neurodevelopmental disorder where symptoms might occur because of inappropriate wiring, then research on the brain of the songbird could turn out to be critical. It is very hard to explain those findings in a sound bite.

Mr. PORTER. I hope you don't find any grants that are frivolous or questionable. I think it is your job as much as ours, to review everything that you do. And I am sure all of you are doing this. Because obviously the expenditure of public funds in a way that is meaningful and useful is what this is all about, and any time that the door is open for criticism, we may be absolutely sure that somebody is going to find the criticism to be made and the media is going to print it.

Dr. HYMAN. I agree. I did not mean I would ever find anything frivolous. What I meant was the breadth of our portfolio is such that there are areas where people might disagree, but I have every faith that there is nothing frivolous.

COMPLEX GENETIC TRAITS IN MENTAL ILLNESS

Mr. PORTER. A collection of studies published last fall identified Chromosome 6 as the location of a gene that puts some people at risk of schizophrenia. Three other chromosomes have also been identified as candidates for a schizophrenia marker. Scientists have struggled for some time to find genetic markers for this disease. Do you think they are finally on the right track? Is a genetic link likely to be responsible for a large share of schizophrenia cases?

Dr. HYMAN. You have asked a question that goes to the heart of genetic research in psychiatric disorders. That gets back to the question you asked about multiple-interacting genes. We have discovered that in serious mental disorders, vulnerability—not a certainty of illness, but vulnerability, does seem to be conferred by different genes or sets of genes in different families, or pedigrees. Second, within any one pedigree, vulnerability is conferred very likely by multiple genes interacting with the environment.

Unfortunately, our task is complicated by the difficulty of making a diagnosis. And in the case of schizophrenia, while a diagnosis might be made with much greater certainty than in some other psychiatric or mental disorders, it is difficult to be certain, so we are factoring in multiple levels of complexity.

While there have been repeated assertions that we have finally found vulnerability genes, we don't have the final answer. I hope this locus on Chromosome 6 is something that leads us to a real vulnerability gene, but what I can say is that the right methodologies are now being employed.

We are beyond the first few years of enthusiasm where we rushed headlong in the hope that these disorders were due to a single gene functioning in some simple way. I would add, one of the great advantages to us at NIH is having the Genome Center and having on the drawing board a new Center for Complex Traits. These new findings and the new, more sophisticated molecular genetics approaches are really models for us as we start to work on

what I think are some of the most challenging problems now facing biomedical science.

Mr. PORTER. We understand that not only have you started a new position this week but you have had a third baby.

Dr. HYMAN. Not quite yet. The baby is due in June.

Mr. PORTER. Our information was not accurate, but on track.

Dr. HYMAN. Just a little premature. I am trying to maximize my stress points.

SPINAL CORD INJURY AND REGENERATION

Mr. PORTER. Dr. Hall, your Senate testimony mentioned evidence that regrowth of damaged spinal cord nerve cells is possible in laboratory animals. We heard public witness testimony this year from Christopher Reeve's brother and others for whom this research finding would be very important. What does this research realistically offer such families?

Dr. HALL. The repair of spinal cord injury, and indeed a brain injury in general is one of the most challenging problems in brain research. As you know, in the brain, unlike the liver, once cells die, they in general do not regenerate and it is not possible to make new cells. If you damage a bit of a liver it regenerates, grows back. That is not true in the brain.

It is further complicated by the fact that the brain has enormously complex connections which are central to its proper functioning. Each nerve cell may receive inputs from as many as a thousand other cells. These inputs are not at random, are put together in a very precise way, and how this occurs is one of the major mysteries of developmental neural biology, how the nerve system gets put together.

What happens in spinal cord injury is that one has to recapitulate the event, rewire a part of the nervous system that has now been damaged and reestablish connections, and in some cases, cells are lost irreparably, and so the nervous system also must then make compensatory circuits which can adjust for those lost cells.

So I think the first point to be made is that this is indeed a daunting problem. We have made some progress. In recent years our understanding of what it is that controls the growth of neurons has increased enormously. Last year we found for the first time a substance which had been postulated for over 100 years, a substance that directs the growth of nerve cells, and a group in California discovered a protein which is responsible during development for directing the growth of nerve cells. This was a foot in the door, and with this protein in hand one can begin to look for other proteins.

One of the things that was found out right away was that in fact this protein not only attracts some neurons but it repels others. So there is a complex regulation involved in establishing connections in the nervous system.

We also know that nerve cells do not regenerate easily in the central nervous system. If you cut a peripheral nerve, a nerve to your hand or arm, you will be without function for some period of time, but that nerve will slowly grow back and reestablish connections, usually imperfectly, but some connection is often reestab-

lished, and one can actually follow the regrowth of the nerve by development of sensation along the lower arm and hand.

The central nervous system axons do not regenerate. It turns out that in part their failure to do so depends on the environment. There is nothing wrong with these cells, they can regenerate, but they are in an environment in which there are substances which inhibit them from regenerating and they lack the normal stimulatory substances that cause them to regenerate.

Another way of putting it is that it is necessary in the adult in these repair situations to recapitulate an earlier time in development when cells in the central nervous system did have the proper environment in which they could grow, and secondly, to make exact connections. What we have learned, mostly about spinal cord injury, I would say involves two different things. First of all, methylprednisolone, a treatment which investigators funded by our institute found years ago could limit spinal cord injury, has the effect of preventing, we think, some of the swelling that normally occurs and therefore decreasing pressure.

And secondly, there is a new concept which we hope will find application there and that is of so-called excitotoxic injuries. When a large number of cells are injured at the same time, either as a result of trauma or in the course of stroke as a result of lack of oxygen, they will release a normal signal in massive amounts and this signal literally excites other nerve cells to death that are in the neighborhood. They receive far too much excitation. They accumulate calcium inside and the cells are irreparably damaged. There is great interest now in a treatment to limit the excitotoxic death, the second wave of injury that occurs after the primary injury.

We hope also that these treatments will soon find their way into the clinic. The problem, however—well, let me back up. The aim of completely restoring function for someone like Mr. Reeve is truly a daunting aim and I think will take some time. However, we know that even incremental changes are often very important to people who have spinal cord injury; that is, even if you don't have fine movement of your fingers, the ability to hold something can make a big difference in the quality of life of people who are injured.

So first of all, even treatments that get us partially along the way have benefit for patients who have spinal cord injury.

Second, I should tell you about a program we have had in our institute for some years called a Neural Prosthesis program, whose aim is to provide aids for those without function. One of the areas in which that has been most successful has been in using muscles that are not damaged, picking up the electrical stimuli from those muscles and using them to drive muscles in the hand through electronic devices so that even if the normal circuits to the spinal cord are not present, one can recreate some of these crude movements. That has been quite successful in terms of crude hand movements and there is just beginning to be work on postural aids that will let people stand upright. Even if you can't run or walk, the ability to stand is of some benefit in these situations.

We are working in these different areas at the molecular level exploring proper factors that simulate growth, at the cellular level at trying to understand the wiring diagrams and how these may be recreated, and also in trying to provide help through these arti-

ficial devices which have now become enormously sophisticated for those with this kind of injury.

REHABILITATION RESEARCH

Mr. PORTER. What kind of interface is there between your institute and the, say, Rehabilitation Institute in Chicago? Do they work directly with you?

Dr. HALL. I don't know that institute directly. I must tell you that this is an area in which my own background is rather limited. I have only slowly begun to become more aware of this field.

I attended recently a meeting of the National Rehabilitation Board at NIH, which is in the Institute of Child Health and Development, and met many of the people in this area. We support some of them through our Neural Prosthesis Program. I don't know the particular Chicago Rehabilitation Institute. I was tremendously impressed with the dedication of these people and the important work that they are doing and would look forward to the chance to find out more about them.

MAD COW DISEASE

Mr. PORTER. Could you help us make sense of the mad cow disease that has caused such a furor in England? What is known scientifically about the possible links between the disease afflicting beef cattle and a human neurodegenerative disorder called CJP?

Dr. HALL. Creutzfeldt-Jacob disease is the name of that disease. It is a fairly rare disease. It is a neurodegenerative disease mostly occurring in older people. It is one of a family of diseases occurring both in animals and in humans that was originally called slow virus diseases. We now know that they occur through a new kind of infectious agent which is not a virus, it is not a bacteria, but it is in fact a protein. It is against the dogma; how can a protein replicate a cell in order to create infection?

The story begins with research in our institute on a disease in the South Pacific called Kuru. Researchers from our institute were active in investigating this disease in the 1950s and early 1960s, and discovered that it was a transmissible disease and that the disease appeared to be transmitted from the brains of infected patients to others, and that the infection took place via a particular custom in the tribes in which the disease was rampant of taking the brain tissue and actually putting it on their bodies and on the bodies of their children. The infectious disease then gained entry through small cuts in the skin and this resulted in transmission of this terrible disease.

It was pointed out that this disease was similar in its pathology to a disease called scrapie, which occurs in sheep. This is similar to so-called bovine spongiform encephalopathy, which is a long name for mad cow disease and is also related to Creutzfeldt-Jacob disease. Fortunately, through the change in the customs the original disease Kuru is virtually extinct in the South Pacific, but research in this area went on to show that in fact the transmissible agent was not a virus but a protein. And active work supported in several locations by our institute and others is now aimed at understanding how an abnormal protein gains entry to the body and

then converts the body's own protein into agents that can transmit the disease and can cause pathology.

Scrapie is a problem in sheep in Britain and in several other countries. For many years the organs of sheep were fed to cows and this was done in some cases without proper precautions. In the late 1980s, it was realized that this was a possible problem and so there were strict rules drawn up for how this might be done.

However, there has been some concern that this might be transmitted to humans. There is a so-called species barrier which makes the transmission difficult. I would say that one is not sure if that is what is going on. What is known is that very recently there have been 10 victims of the disease. What is striking about these people is that they are young, under the age of 40, which is not characteristic of Creutzfeldt-Jacob disease. In fact, the number of cases of people with diseases like this who are young is very small. So this has raised the suspicion that it might be due to this transmissible agent.

We at present have no evidence of whether it is due to transmission from sheep to cows to humans through cows eating sheep organs and humans eating beef. There is no direct evidence of that. But it is at least a possibility and suspicion and it is this concern that has wreaked havoc in the agricultural economy of Britain.

Mr. PORTER. So if you were in a British restaurant, you probably wouldn't order beef today?

Dr. HALL. Well, let me not comment on that. There is no evidence actually that the material is present in muscle, and there is no evidence that it is transmitted by eating except in very, very high amounts. So it remains to be established what the chain is. According to current knowledge, I think it is unlikely that it occurs through eating beef, but we have no certainty.

Mr. PORTER. Thank you.

NEW DRUG DESIGNS

Dr. Leshner, in February researchers at Duke reported that they had created a strain of knock-out mice in which the gene for the dopamine transporter is eliminated. Their work is thought to be an important breakthrough in studying addiction because drugs of abuse work through the dopamine system and the mice without the dopamine transporter seem to be unaffected by cocaine and amphetamines. What does this animal model suggest in the design of new drugs for treating addiction? Is it possible that the knock-out mice also could help in treating Parkinson's disease, which is associated with dopamine levels in the brain?

Dr. LESHNER. Let me say that the presence of this knock-out mouse as a tool just by itself is a tremendous breakthrough, because it was able to demonstrate what we will call the obligatory nature of the dopamine transporter for cocaine to have some effect; that is to say, that the dopamine reuptake transporter which we have known to be a major site of cocaine's actions is now known to be a necessary site for some of cocaine's actions.

What that means is that when we target our medication development efforts, we want to be targeting it towards the dopamine transporter, and I can tell you we are doing that. Sadly, the transporter is not the only site at which cocaine exerts its effects. It has

effects on the transporter and on the synapse. We spoke before about the D-1 and the D-2 dopamine receptors and their role in cocaine addiction. We are actually directing our cocaine medication development efforts at a variety of sites where cocaine seems to be having its effects. But again, the knock-out finding is tremendously important.

It also was very important to demonstrate the centrality of the dopamine transporter for amphetamine actions. The knockout mouse is also very important because it helps us understand other disorders by providing new insights into the regulation of dopamine neurotransmission. One point is that we all benefit tremendously from the basic research done by other institutes at times for other disease-related functions. It informs us as well.

So to answer your question, I believe that understanding dopamine transmission in its full complexity is going to be tremendously important not only to understanding Parkinson's disease but also schizophrenia, depression, bipolar disorder and all aspects of addiction. These kinds of findings, at a minimum are tremendously important for the specific targets that they are directed at, and also have broad kinds of implications.

Mr. PORTER. We are delighted to welcome also our colleague from California, Nancy Pelosi. I have been in the process of asking questions of each of our directors and will ask another few questions and then I will be happy to call on you for questions.

RECEPTOR SITES

Ms. PELOSI. Thank you, Mr. Chairman.

Mr. PORTER. Dr. Leshner, NIDA-supported research at Yale University has identified important receptor sites in the brain that either suppress or trigger cocaine seeking. Research into receptor sites associated with cocaine abuse has been conducted for some time. What makes these new results important and what treatment implications do they suggest?

Dr. LESHNER. Once again it ties to the fact that cocaine seems to be working through many different mechanisms simultaneously. That is good news and bad news. The good news is it gives us multiple targets to go after. The bad news is it gives us multiple targets that we have to go after.

For example, we know that not only does cocaine work on the dopamine reuptake transporter but it also acts on the serotonin reuptake transporter. We have learned over the course of the last few years a tremendous amount about these sites.

In the study that you mention, what you see actually is the product of very sophisticated neuroscience and behavioral research coming together and is a very good example of how animal models of drug abuse interaction have been tremendously productive. That is, this uses a quite sophisticated behavioral paradigm developed in animals to discriminate between the effects of cocaine on the seeking of drugs and to begin to look at the relapse to cocaine use of people who have stopped using cocaine.

What you see in the study is a very fine level of discrimination between the effect on one kind of dopamine receptor and another kind of dopamine receptor. There are of course more than two receptors to dopamine in the brain, but what this study does is to tell

us that if we want to suppress cocaine-seeking behavior, in this case, in individuals who have stopped using cocaine, we then trigger the dopamine 1 receptor; whereas if we had triggered the dopamine 2 receptor, we would lead to an increase in cocaine seeking.

These kinds of approaches are early. It is one kind of a biological target that our medication development effort is attacking, but it is a very important kind of finding for us.

ALCOHOLICS ANONYMOUS (AA)

Mr. PORTER. Thank you.

Dr. Gordis, the news reports covering the 60th anniversary of Alcoholics Anonymous last year stated that despite the participants' contention that AA is effective, there is little empirical scientific evidence with case control studies that demonstrate AA leads to sobriety. The articles also highlighted the high dropout rates in AA programs. What work has your institute done to evaluate the AA approach and how do you interpret these findings?

Dr. GORDIS. AA has been around for 60 years since its founding in 1935. Having been a director of an outreach and treatment program for many years before I came to Washington, I should preface my remarks, which are those from the scientific viewpoint, with one or two personal observations, if I may. AA is probably one of the supreme human creations of the 20th Century. The genius which has permitted it to survive for 60 years by avoiding so many organizational mistakes is remarkable. The generosity of AA members with their single-minded focus of helping each other to get sober, with the emphasis that by helping others to become sober they are helping themselves, not because of some noblesse oblige is equally remarkable. This focus has its roots in historical movements before AA, such as the Oxford movement. In the program that I ran for so many years, AA was a very important component of our counseling efforts.

But now to get to your question. Has AA been subject to the kind of rigorous outcome analysis which all treatment deserves? The answer by and large is very limited.

First of all, there are certain problems with anonymity, one of the features of Alcoholics Anonymous. This makes certain kinds of recordkeeping very difficult to do. Second, there is a well-known principle in science that if the tools of observation destroy the phenomenon you are watching, you are not likely to learn terribly much. Because the meetings tend to be somewhat private, some of the observational techniques we might use in a hospital setting, therefore, would not be appropriate because they will destroy the quality of the meetings which we would be trying to observe.

Having said that, we have done several things to try to get to the question you are asking. We had a small working conference about 3 years ago on how that very issue can be addressed. A monograph which included several very thoughtful papers on how AA research issues can be addressed resulted from this conference. Some progress has been made, but the fundamental question that you are asking may not be altogether answerable by current techniques, for the reasons I have said.

AA itself however has matured considerably, and 5 or 6 years ago the Intergroup Office in New York published their own survival curves for AA meetings and attendance at AA meetings. Their own data showed that after a period of 2 or 3 months, the attrition rate is very high. It doesn't mean that some people don't come back and make it on the second or third try, but it does mean that even AA has major problems with attrition and relapse, which plagues the whole field of alcoholism and drug abuse treatment. This is the central research target we are trying to conquer.

I must say that I admire the fact that AA did publish these data. They are cognizant of the fact that they have to do much more to retain people very early on in treatment. But it points to the fact that despite its glories, AA is only part of the answer to the alcoholism treatment issue. After 61 years, they probably reach less than 10 percent of the total alcoholic population of the country. AA therefore remains a terribly valuable part of most treatment programs, but clearly the kind of research which I alluded to in my introductory remarks, the development of new pharmacotherapy based on neuroscience, is the wave of the future. So we need both.

Mr. PORTER. I have to say that you know and we know that alcoholism affects practically every family in the country one way or the other. I had an uncle who was an alcoholic right out of "Lost Weekend" and went to AA, and never had another drink again for the remainder of his life, which was about 20 years. So anecdotally at least, I am a great believer in the possibility of real help for people.

Dr. GORDIS. So am I, because I have seen it so often in my own career. But as a scientist, one must look not only at the anecdote but at the whole picture, and I think what I said to you is fair.

FETAL ALCOHOL SYNDROME

Mr. PORTER. Research findings reported in January suggest that babies born to women who drank alcohol during the last 6 months of pregnancy were 10 times more likely to develop leukemia during infancy. This would seem to rekindle the debate about whether any alcohol consumption at all is safe during pregnancy. What is your personal view about this, and does your institute offer any official advice to pregnant women?

Dr. GORDIS. I haven't read the original paper on the leukemia finding to which you allude, only reports in the press. It is a very rare disease to start with, and the findings were promising but very early and have to be confirmed. The question that applies to pregnant women goes far beyond the occurrence of a very rare infant disorder. We are talking about the effect of alcohol on brain development, on neuro, psychological and intellectual development of children after birth, and in cases of very marked excess alcohol consumption, the picture of fetal alcohol syndrome, which is a group of actual visible malformations.

For every one of the kids who has died, there are probably 10 or 12 others who are susceptible to getting defects in intellectual and emotional development that are not manifest as physical defects. The question that you are raising is based on the question that is often asked us. Is there a threshold below which one can assure women that there is no likely risk from alcohol? The answer in my

view, and I think the science supports it, is that we don't know of any such threshold. As a result of research done by NIAAA investigators, such as Sandra Jacobson in Detroit and others, using the most sophisticated kinds of epidemiological research and tools of cognitive neuroscience and psychology, we now know that the dose at which one can see subtle effects of cognition and intellectual development is far less than the dose that alcoholics drink. We are down to a level of one or two drinks a day.

Since we have such wide biological variability to susceptibility, the only responsible advice that I believe one can give pregnant women is not to drink at all.

Mr. PORTER. Thank you, Dr. Gordis.

Ms. Pelosi.

BEHAVIORAL SCIENCE RESEARCH

Ms. PELOSI. Thank you, Mr. Chairman.

Please forgive me for not being here. We had a memorial service for Don Turner, one of the people on Secretary Brown's plane. He was from my district. Only that would have kept me from this very important hearing.

I understand that you have covered a great deal of territory in the course of the afternoon, so don't fear, I will not keep you here much longer. In fact, I was going to ask about fetal-alcohol syndrome, but I don't think I have to now.

One other question that I raised at a previous hearing last week is—first, I want to commend you for the report basic behavioral science research in mental health, a national investment. As you may know, this report was circulated to all the Members of Congress by a number of us under the leadership of our Chairman, Mr. Porter and Mr. Obey. My question springs from that report, just briefly.

What are we going to do to encourage the training of behavioral scientists for research in substance abuse?

Dr. LESHNER. First of all, let me start by saying that the drug abuse arena, in particular, has had a very long and productive history of behavioral science research. It is behavioral science research that has given us many of our newest and most efficacious behavioral treatments. They are the translation of basic science findings into practical settings.

In addition to that, basic behavioral science research has given us a wonderful set of behavioral models from which to study all aspects of drug abuse interdiction, including medication development and the way in which drugs work on the brain. Those techniques have been developed because of the interplay between neuroscience and behavioral science.

Having said that, when I became the NIDA Director 2 years ago, as I looked through the portfolio, I became concerned, as I have in other areas, that there were some gaps in what we know about drugs of abuse and what to do about it, and some were in the behavioral science arena. Therefore, we have tried a couple of things in order to attract some new scientific, mostly basic behavioral, research, into our portfolio.

One, we issued a Request for Applications called Beyond Traditional Paradigms, or new behavioral science research, basically re-

questing research in areas that have not traditionally been the center of our research. For example, cognitive science is an area where we have not done that much. We were disappointed; we didn't receive a very large number of outstanding proposals from senior people, so we have gone after young people.

What we are trying to do now is to attract young scientists into our domain so that they will see the tremendous opportunities because of these gaps that exist in behavioral science with drug abuse and addiction.

BRAIN AND DRUGS

Ms. PELOSI. Do you think it would be an imposition on the committee time, Mr. Chairman, if I could have an explanation of the charts since somebody went to the trouble of making these charts?

Mr. PORTER. That is a question for Dr. Leshner as well.

Dr. LESHNER. Thank you. I will be brief.

This top chart is what we call "Your Brain on Drugs." What it actually is showing you is the time sequence of PET scans of the same individual's brain over time. You are looking at radioactive cocaine being concentrated into the striatum. First of all, we have identified the receptors and the mechanisms of action in the brain for every major drug of abuse.

And secondly, we actually have ways now to understand and to talk about drugs, the effects of drugs on the brain that go beyond inexact metaphors like "fried brains," and so forth. We have a tremendous amount of information.

The second chart we have been calling "Your Brain After Drugs." What you see is, on the top line, three slices of the brain of a normal individual. This is metabolic activity in the brain. The second line shows you a very heavy cocaine abuser 10 days after that individual has stopped using cocaine. The third line shows the same individual 100 days later. The point here is to demonstrate that prolonged drug use produces fundamental and very long-lasting changes in the brain at many levels. We also know some of those changes are at the cellular level. We believe those brain changes underlie addiction, that is to say, that addiction is a brain disease that comes about as a result of the brain being changed in fundamental and long-lasting ways by drug use.

You have the brain on drugs, then the brain after drugs: this third chart is the memory of drugs. What you see here is a very important example of the combination of behavioral science, sophisticated behavioral science and neuroscience. On the right side you see what happens to the brain of a cocaine addict who is not at the moment taking cocaine, when that individual is exposed only to drug paraphernalia that are associated with the drug use. We know that not only the drug but the circumstances surrounding drug use become a condition of the addiction. When the individual watches the cocaine video of the paraphernalia, it is producing craving in the individual and lighting up the part of the brain where conditioned emotional responses occur. On the left side the same individual is being exposed to something that does not cause craving. The same area does not light up. It is a very important demonstration because, you can see, using these advanced technologies, you can look into the brain of living, breathing, behaving

individuals and begin to get a much finer grain understanding of what is going on in the brain as behaviors are occurring.

Ms. PELOSI. And one can then conclude from that that we can still rehabilitate people who have had a serious addiction but we have to make extra effort because—

Dr. LESHNER. There is no question that addiction is a treatable illness. We have hundreds of studies to demonstrate the effectiveness of treatment. The issues have to do with matching individuals to particular forms of treatment which will be the most effective for them. These kinds of things demonstrate the complexity of addiction as a phenomenon, i.e., it is a brain disease expressed in behavioral ways for which the social context is very important. The most effective treatment will of course combine the three elements, the biological approach, the behavioral and the social context approach.

We are working through our research programs to make sure that those combined integrated approaches are in fact being developed, because all the evidence suggests that they will ultimately be the most effective treatment we have.

PREVENTION

Ms. PELOSI. I find that very interesting, and I am encouraged by your conclusion. But I think in terms of prevention, if our young people can see the path they are choosing, that it is not mind over matter and that they can not stop any time they want and that it does have residual implications, that it might be useful for them to see that as well.

Dr. LESHNER. We in our Department under Secretary Shalala have been mounting a major education campaign around a variety of drugs of abuse, particularly marijuana and some of its effects on the brain. In addition, we have been working closely with the Partnership for a Drug Free America and other organizations that do far more public education than we do in order to make sure that the messages that are being relayed are scientifically credible, accurate, and do reflect what we are learning very quickly about what drugs of abuse actually do.

Ms. PELOSI. I appreciate that.

Mr. Chairman, I don't have any further questions, or I have 100. But in the interests of time, I just want to close by saying how important I think the representatives who are here today are. We all know how preventing disease and finding cures for disease is important to our country. But in terms of mental health and addiction, as you so clearly pointed out, they have tremendous impact on every family in America.

So I want to commend Dr. Varmus and all of his colleagues today for the work that they do and for making this testimony available to us. I wish that I could be here for it all, but I am most certainly going to get a report on it. Thank you very much.

Mr. PORTER. Thank you, Ms. Pelosi.

Dr. Varmus had a comment on one earlier question, did you not?

Dr. VARMUS. Yes, if I could beg your indulgence. I just wanted to expand on one of the questions asked of Dr. Hall about the use of 1 percent transfer authority for this year to benefit neurosciences.

We had an opportunity, due to the very generous appropriation we received this year, to initiate extra work in the neurosciences, to advance before 1997 areas of research that we had targeted for that year. In addition, the appropriation allowed us to fulfill some of the requests that were in the Senate report language with respect to degenerative diseases of the nervous system.

What I did was to transfer money, \$7.8 million, to the Neurology Institute with instruction that the four institutes represented here and the National Institute on Aging form a consortium to consider how to spend that money and to match it with an equal \$7.8 million. They considered a variety of proposals. They recommended to me proposals for research in a variety of areas of neuroscience pursued by all five of the relevant institutes. Most of the money was in fact in areas of degenerative diseases—Alzheimer's disease, Parkinson's disease, and developmental neurobiology—which of course has a direct bearing on degenerative diseases. So, in total, \$15.6 million has been advanced in a special initiative in the area of neuroscience and getting us in advance of 1997 initiatives.

Mr. PORTER. So if I understand you correctly, the increases that NIH has received have been used to respond to Senate requests; is that correct?

Dr. VARMUS. You are making me feel slightly embarrassed, Mr. Porter, but I will get over that. We feel that our own objectives have coincided quite nicely with the interests of our Senate appropriators.

Mr. PORTER. Let me thank you, Dr. Varmus, and each of the four directors who are witnesses today. The testimony has been extremely fascinating and informative, and we think each one of you did an excellent job.

I tried to ask the questions in as even a way as possible and give each of you a chance to testify about the matters before each of your institutes. I don't know whether we could say that this has been a success, but we will have a chance, I think, to try it out on another panel here later on, and we will—

Dr. VARMUS. We have one other panel, Mr. Porter, and that is going to be on Friday.

Mr. PORTER. And we are not in session that day, either. So Nancy and I will be here to work with that panel. But we will have to see how it works out. I think it worked very well today and we covered a great deal of ground, and I hope each of you got as much out of it as I did. I want to thank each one of you for the fine job that you are doing at NIH. Thank you all. We stand in recess until 10 a.m. tomorrow.

[The following questions were submitted to be answered for the record:]

QUESTIONS SUBMITTED TO THE PANEL

NEUROSCIENCE RESEARCH GOALS

Mr. Porter: Is there any mechanism at NIH which the leadership uses to broadly set budget goals for funding various types of neuroscience research across individual institute budgets?

Dr. Hall: NIH has no formal mechanism for setting budget goals for neuroscience research across the Institutes and Centers (ICs). The setting of research/budget goals is an ongoing process within the NIH and takes place at two levels -- the Institute or Center Director, and the Director of NIH, with whom ultimate responsibility lies for the course of federally funded medical research. This system was established because of NIH's strong commitment to an integrated approach to developing and implementing research priorities. Rarely does a disease affect an individual organ or body system exclusively; this complexity is a reflection of the body's intricate network of interacting organ systems. Consequently, it is rare for a single IC--with its particular research focus on a disease category, body system, stage of development, or area of science--to be the sole supporter of research on a given field of science. It is more likely that one IC will serve as the lead for coordinating the efforts of, and ensuring communication among, the various institutes that study the diverse aspects of a complex disease or area of science. This is certainly the case for neuroscience research, which transcends nearly all IC boundaries.

The NIH Director has available two mechanisms to highlight and supplement particularly exciting or urgent areas of research, such as neuroscience, that span many ICs. They are the Director's Discretionary Fund and the Director's authority to transfer up to one percent of the total NIH budget among the Institutes and Centers. Use of these mechanisms involves extensive consultation with the ICs to identify research initiatives which reflect NIH-wide priorities. For example, following the enactment of FY96 funding for NIH, the Director identified several research areas that might benefit from additional stimulus, including an expansion of the "Biology of Brain Disorders" initiative. A consortium of five ICs -- National Institute on Aging (NIA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), and National Institute of Neurological Disorders and Stroke (NINDS) -- was formed to recommend allocation of \$7.8 million to be provided for neuroscience research. Funds provided through use of the transfer authority are to be matched by the ICs, providing a total of \$15.6 million in funds to be transferred among and within IC budgets to support this initiative. The goal is to jump-start selected areas of the "Biology of Brain Disorders" initiative in anticipation of additional growth in FY97. All ICs were invited to propose meritorious projects for funding within the \$7.8 million. On the basis of this trans-NIH competition, \$4.2 million was allocated for research on neurodegenerative disorders, which after matching funds are provided, gives a total of \$8.4 million. Another \$1.6 million goes toward research on development of the nervous system -- this work has implications for the ability of the adult brain to repair and reorganize itself following injury from stroke, trauma, or degenerative processes.

The remaining funding for neuroscience research is being allocated on a matching basis among National Eye Institute (NEI), National Institute of Child Health and Human Development (NICHD), National Institute of Mental Health (NIMH), and National Institute of Neurological Disorder and Stroke (NINDS).

SUPPORT OF NEUROSCIENCE RESEARCH

Mr. Porter: Perhaps this is a question for Dr. Varmus more than the Institute Directors. A devil's advocate could look at today's panel and suggest that rather than artificially separating neuroscience research into these four institutes (and the aging institute, which is not here today), it would make more sense to consolidate their efforts into one neuroscience group, since they are all examining the same fundamental cellular processes. How would you respond?

Dr. Varmus: Organizing NIH along scientific disciplines, such as cell biology, molecular genetics, immunology, and neuroscience, has been proposed in the past, but there was strong concern that such a format would diminish the human health focus and comprehensive approach to addressing complex diseases that NIH currently has. One of NIH's greatest strengths comes from the fact that each IC has a clearly defined health research mandate, which is often focused around a disease category, body system, stage of development, or area of science. This enables NIH to bring to bear the multidisciplinary research approaches necessary to address the many complex health problems faced by our citizens. Thus it is customary, and, indeed preferable, that several ICs address the different areas of science that relate to a given disease or condition.

Moreover, just as the nervous system interacts with all body systems, nearly all NIH ICs--not just four or five--participate in neuroscience research. The diversity of specialties required for this research and the fact that many diseases bridge the missions of multiple ICs make neuroscience a cross-cutting activity at NIH. One example of the scope of neuroscience is illustrated by a simple statistic: a recent inventory of NIH funding documented the involvement of virtually every NIH IC, for a total of almost \$2 billion, or about 18 percent of the total NIH budget. Even from a genetic perspective, neuroscience is virtually all-encompassing; it is estimated that half of the genes in human DNA are brain-related, testifying to the enormity of the task of understanding the brain.

It should also be emphasized that, based on its mandated mission, each NIH Institute or Center brings its own unique perspective to the neuroscience research it supports, resulting in synergies that everyday are yielding a more complete picture of how the brain functions. These advances arise from the extensive communication and collaborations taking place among the ICs carrying out neuroscience research. Some collaborations are informal in nature and others are guided by inter-institute committees or by NIH-wide coordinating offices. Several established mechanisms foster cooperation among NIH ICs in the neurosciences. Among these are joint efforts in large programs like the Human Brain Project, coordinating committees on Alzheimer's disease and Parkinson's disease, joint program announcements,

cooperative sponsorship of workshops, less formal regular meetings on particular diseases, frequent communication among the IC Directors and program staffs of the different ICs, and extensive collaboration among intramural researchers.

One final consideration is that most of the ICs proposed for consolidation have research portfolios which include a significant number of extremely important studies that are outside of neuroscience, yet are a vital component of their mandated research missions. For example, the NIAAA supports investigations of the effects of alcohol on the liver, NIA carries out studies related to preventing fractures and other serious health problems associated with frailty in the elderly, the NIMH supports research on suicide and violence, and NIDA has a strong commitment to the prevention of drug abuse. These and many other research areas conceivably would not fall within the purview of a neuroscience institute. At the same time, these research areas are equally critical to improving health and must continue. Consequently, consolidation would ensure neither more productive science nor more rapid advancement of human health.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

INTRAMURAL RESEARCH PROGRAM

Mr. Porter: Dr. Hall, you have appointed a new chief for your Institute's intramural program and I understand a review of the intramural program is underway. What issues have you highlighted for the review? What is your vision of the proper size and research focus of your intramural program?

Dr. Hall: We are in the process of reviewing the intramural research program at NINDS. At present the review is being conducted internally, but we anticipate that like NIMH we will also have a review by a blue-ribbon external panel. To assess our program, the new Scientific Director has met with all the Laboratory and Branch chiefs and each of the tenured independent scientists. In addition, we are taking advantage of previous external reviews of the Laboratories and Branches that are conducted by the Board of Scientific Counselors, a group of outstanding extramural scientists, every four years. In some cases, reviews of particular units are being expedited to provide more information for our internal assessment.

The principal issues being addressed in the reviews are the excellence of the individual research programs and their promise for important new insights into nervous system function and dysfunction. NINDS has an outstanding history of basic and clinical neuroscience advances. For example, our scientists discovered the cellular basis of the blood brain barrier which protects the brain and the cellular mechanisms responsible for release of neurotransmitters at synapses. Similarly, NINDS scientists were responsible for elucidating the transmission of kuru, a neurodegenerative disease very similar to mad cow disease, and for identifying the genetic defect in Gaucher disease and developing a very effective replacement therapy.

The goals of the present review are: 1) to identify outstanding programs already in place and determine the appropriate level of support; 2) to identify programs already in place that are important but would benefit from the incorporation of new research approaches and/or personnel and strengthen them; and 3) to identify new research opportunities that could be accomplished profitably in the intramural research environment. Our initial assessment is that the present size of the intramural research environment is appropriate, but that reallocation of resources among different research programs and the investment in new, particularly exciting or promising initiatives would significantly enhance the contributions of the intramural program.

RESEARCH FUNDING AND NIH PRIORITIES

Mr. Porter: Is there any process by which the NIH leadership looks at spending across all the Institutes to consciously decide if the total allocated to cross-cutting diseases like Alzheimer's is consistent with overall NIH priorities?

Dr. Hall: There are several ways in which NIH evaluates research spending and priorities. The most formal assessment occurs in the annual budget process, when areas of special emphasis are identified prior to the submission of the President's budget request. This provides an opportunity for the Institutes and Centers to propose and justify increases for areas of special priority and for the NIH Director to consider both the proposals and any associated program adjustments for all components at once. A similar process occurs when additional funds become available or resources are redistributed, for example, in the allocation of funds under the Director's one percent transfer authority. During the past two years, the institutes concerned with research on the brain have found these interactions particularly helpful in establishing consensus on areas of particular need and opportunity.

Interactions among scientific staff occur at several levels, based on common scientific interests. These include purely scientific exchanges through rather informal "interest groups," most of which are based in the intramural program, as well as more formal committees concerned with such topics as Alzheimer's disease, Parkinson's disease, and sleep research. The latter groups facilitate the coordination of extramural initiatives such as program announcements and workshops.

The more challenging problem is the identification of priorities. In reviewing the effort and resources devoted to crosscutting diseases, the NIH faces a problem analogous to that faced by individual Institutes and Centers—that is, the need to balance scientific opportunity and public health concerns. To address this need, the NINDS and the Office of the NIH Director interact in a variety of ways: through our budget office and science policy office, which have counterparts in the OD, and with a variety of central offices and trans-NIH committees on which our scientific or science policy staff serve. We find that this structure allows for a unified approach while incorporating the scientific and policy concerns of the Institutes and Centers.

PARKINSON'S DISEASE

Mr Porter: I know that your Institute has accelerated its involvement in Parkinson's disease research, and it seems as if a number of promising research leads have been reported. What is your assessment of the present state of scientific knowledge relating to Parkinson's disease?

Dr. Hall: The cause of Parkinson's disease is unknown, and there is no cure. Advances in basic neurobiology are leading to better understanding of this disease and to new strategies for treatment. However, Parkinson's is a complex disease and there is no definitive cure on the immediate horizon. Progress is likely to occur in steps and will require efforts on several basic and clinical fronts.

The death of brain cells that use the signaling molecule dopamine is responsible for most of the symptoms of Parkinson's disease, but why these cells die has been a mystery. There is now increasing recognition that similar biological mechanisms contribute to the death of brain cells in many neurological diseases, and several of these interacting processes have been specifically implicated in Parkinson's disease. Among them are oxidative stress (damage by free radicals), excitotoxicity (harmful effects from excessive levels of normal signaling molecules), and calcium mediated damage. Because many neurodegenerative diseases share mechanisms of underlying damage, research about and treatments for one disease may prove useful for many diseases.

The recognition that cells help regulate their own fate and may invoke "suicide" programs is also an important insight into degenerative diseases. We are just beginning to understand the normal biology of the signaling factors that control cell fate and how these signaling systems go awry in disease. Trophic factors (cell survival molecules), for example, have recently shown promise for ameliorating the effects of dopamine cell loss in animal models of Parkinson's disease, but we need to learn more about the basic biology of these signaling factors and to overcome practical problems before such signals can be used for human treatment.

While several biological processes have been implicated in Parkinson's disease, the trigger for the disease is unknown. Toxins and viruses can cause Parkinson's-like disorders, and population studies suggest that environmental factors may play a role in some cases of Parkinson's disease. In spite of considerable research effort, however, no environmental factor has been implicated in the majority of Parkinson's cases. Defective genes can cause Parkinson's disease, although it is not yet clear what proportion of Parkinson's disease is hereditary. Regardless of what percentage of Parkinson's disease is inherited, finding the genes responsible for familial Parkinson's should help to understand all forms of the disease. This has proven to be so, for example, for Alzheimer's disease and Lou Gehrig's disease. Techniques now available should allow researchers to identify the genes responsible for familial Parkinson's disease in a relatively short time. NINDS has recently begun the search in collaboration with the Human Genome Center. With the gene in hand, the tools of molecular biology may reveal the cause of Parkinson's disease.

A variety of new therapies for Parkinson's are under development; some may become available in the short term while others will require long-term research. Standard medical therapy for Parkinson's disease alleviates symptoms by using the dopamine precursor levodopa to replenish the dopamine lost with the death of brain cells. Efforts are continuing to refine this approach and to reduce the development of adverse effects which eventually limit the usefulness of levodopa for most patients. Trials of surgical therapies are also underway. Surgery attempts to restore the balance between movement-inhibiting and movement-activating circuits in the brain. Although surgery was tried in the past with mixed results, now surgeons can use the behavior of individual brain cells, recorded with microelectrodes, as signposts to precise locations in the brain.

The encouraging early results from these improved surgical therapies have led to systematic clinical trials. Attempts to replace dopamine cells by transplantation of fetal tissue are also ongoing; this procedure has provided benefits to at least some patients. Transplants of cultured cell lines and stem cells should eventually replace fetal tissue, but better understanding of basic biology will be necessary before this is possible. Finally, gene therapy using transplantation of genetically engineered cells or direct insertion of genes into patients' brain cells may become clinically useful in the future, but, again, basic research is needed before this becomes feasible. Improved understanding of the biology of Parkinson's disease is leading to better ways of relieving the symptoms of Parkinson's patients and ultimately halting the underlying degeneration of brain cells.

HUMAN BRAIN PROJECT

Mr. Porter: I assume all of your institutes are involved in the Human Brain Project. Could you describe the objectives of this interdisciplinary project, and which Federal agencies beside NIH are involved?

Dr. Hall: The Human Brain Project is currently sponsored by 16 Federal organizations, two of which joined in the last year. The NINDS, along with all of the Institutes that took part in the Brain and Brain Disorders Panel in the Appropriations hearings are participants. NIMH is the lead organization and coordinator for all Federal agencies, NIH institutes, and the university and Federal laboratory supercomputer and information science communities participating in the Human Brain Project. In addition to the NINDS and the NIMH, the NIH members include: the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Dental Research (NIDR), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Library of Medicine (NLM), and the Fogarty International Center (FIC). The other participating federal agencies are: the National Aeronautics and Space Administration (NASA), the Department of Energy (DOE), the Office of Naval Research in the Department of Defense (ONR/DOD), and the National Science Foundation (NSF). Representatives from all of these organizations comprise the Federal Interagency Coordinating Committee on the Human Brain Project (FICC-HBP), which coordinates, funds and steers this effort. The coordinating committee precludes unnecessary duplication of effort across Federal organizations and has significantly enhanced the value of the research supported under this initiative. International interest in the project has been expressed by numerous organizations, and efforts are under way to coordinate such research globally.

The Senate requested an update on the progress of this effort (Senate Report 104-145), which is presented in the Congressional Appropriations Committee Report: The Human Brain Project: Forging the New Science of Neuroinformatics.

The long term goal of the Human Brain Project is to provide the means to integrate coherently and comprehensively the vast, diverse and complex data generated by brain and behavioral research. This will increase the efficiency of brain and behavioral research and will accelerate progress in understanding the puzzle of brain function in illness and health. The Human Brain Project supports neuroinformatics research, which knits together the edges of two rapidly advancing and broadly defined areas of science: brain/behavioral science, and informatics, drawing from fields such as information science, computer science, applied mathematics, and engineering. Neuroinformatics is a new area of science, and the Human Brain Project is playing the principal role in its development.

BATTEN DISEASE

Mr Porter: This year, as in the past, we heard wrenching testimony from a family with two children afflicted with Batten's disease. They stated that NINDS funding of Batten's research had dropped 20% from 1994 to 1995. What was the reason for this drop off in funding - have you seen a reduction in fundable applications?

Dr. Hall: In the past year, the gene defects for two forms of the neuronal ceroid lipofuscinoses (NCL) or Batten disease were discovered; the infantile form and the juvenile form.

Once investigators discover a gene linked to disease, research approaches to the disorder may need to be opened up, redirected, or abandoned. Several grants were not funded for FY95 because, in light of the new genetic information, the research proposed no longer appeared appropriate. As a consequence, funding levels decreased, but our commitment to research on NCL remains unchanged. We have communicated with these researchers who are redirecting their research proposals in light of the dramatic genetic findings. Further, a new grant has been funded to determine linkage and find the gene for another form of NCL, the late infantile form. The NINDS will also be reissuing a program announcement on the NCLs updating the program announcement to take into account the new findings and the new lines of investigation that can now be pursued.

NEUROFIBROMATOSIS

Mr. Porter: We understand that the neurofibromatosis (NF) research field has produced some important discoveries in the past several years and is poised to make advances in treatment. What level of support do you plan to commit to NF research in 1997, including any joint efforts with other Institutes?

Dr. Hall: The NINDS serves as the lead Institute at NIH for research on neurofibromatosis as a major neurological disorder. In FY 1997, the estimated budget for NINDS-supported neurofibromatosis research is \$5.311 million. The Institute will continue a program announcement, in conjunction with the National Cancer Institute, to encourage the submission of research grant applications in all aspects of neurofibromatosis research. The staff from the two Institutes will work cooperatively to facilitate project review and funding. In another ongoing program announcement, the NINDS encourages research applications concerning neurogenetic disorders of infancy and childhood, and specifically cites neurofibromatosis as a disorder of interest. In the past, sponsors of an annual workshop on neurofibromatosis have successfully competed for partial funding and co-sponsorship of the workshop by NINDS. This open workshop deals with topics that include clinical aspects, molecular genetics, animal models, and therapeutic approaches for NF. The Institute will continue to consider applications for partial support of such workshops.

Mr Porter: Last year's House report suggested that you consider issuing, an RFA for NF research. Do you think this is a good idea?

Dr. Hall: While we have not ruled out the use of an RFA or an additional program announcement related to NF, we do not consider it necessary or desirable at this time in view of the investigator-initiated efforts which have been so productive. In just the past five years, scientists have identified the genes for both NF1 and NF2, as well as the gene product that each encodes - *neurofibromin* and *merlin*, respectively. The genes for NF1 and NF2 have been cloned, and knock-out mouse models have been developed for both NF1 and NF2, presenting greatly expanded research opportunities. The vitality of the ongoing research in the area of neurofibromatosis is impressive and holds the promise of even more advances.

We are, however, very interested in an exciting development from the Cold Spring Harbor Laboratory's Banbury Conference on "Neurofibromatosis: How to Develop Therapies" held October 15-18, 1995. As a result of the conference, the NF community of basic scientists, clinicians, and representatives of large pharmaceutical firms has decided to establish small working groups whose charge is to solicit consensus opinion on research needs in NF, particularly in translational and clinical research, and develop recommendations that would be submitted to the NIH. We look forward to meeting with representatives of the neurofibromatosis research community to discuss those recommendations. It is anticipated that the appropriate NIH Institutes would work individually, or together, as appropriate, to develop the most effective approach for addressing these identified research needs, using input from the working groups. This approach has some very exciting possibilities, since it originates with the involved research community, and the NIH experience has found investigator-initiated research to be a most productive avenue of discovery.

DYSTONIA

Mr. Porter: The funding level for dystonia research appears to have dropped from 1994 to 1995. Is this the result of fewer high quality applications or a shift in Institute priorities? What strategies might you pursue to increase the resources allocated for dystonia research in the coming year?

Dr. Hall: Research on dystonia remains a high Institute priority. However, in the past fiscal year, the number of high quality research applications received by the Institute has decreased resulting in a lower overall funding level. To stimulate applications in this area, the Institute has promoted the distribution of a Program Announcement soliciting research in dystonia, and has continued to work closely with investigators and voluntary organizations to increase interest in dystonia research. The NINDS Intramural Research Program is also conducting research on dystonia that involves: (1) quantification of the deficits using a piano key pressing paradigm, (2) the use of transcranial magnetic stimulation of the human motor cortex to assess the relative importance of the central inhibitory and excitatory mechanisms in producing dystonia, and (3) evaluation of the contribution of sensory information in producing dystonia using microneurographic recordings from human nerves.

Mr. Porter: Will dystonia research be part of the neurological diseases initiative begun with Dr. Varmus 1% transfer authority?

Dr. Hall: The dystonias were not specifically identified as part of the research to be supported by the 1% transfer initiative. However, an important component of that initiative provided support for basic studies in developmental neuroscience with emphasis upon understanding factors which control the development of the intricate neuronal connections in the brain and allow plasticity. Such research could shed new light on the causes of the dystonias which seem to involve abnormal interactions between excitation and inhibition in specific areas of the brain.

FUNDING FOR SPECIFIC DISEASES

Mr. Porter: Identify FY95-97 direct (versus related) spending for the following: Gauchers's Disease, Duchenne muscular dystrophy, Alzheimer's disease, Huntington's Disease, multiple sclerosis, head injury, stroke, epilepsy, Batten Disease, neurofibromatosis, dystonia, postpolio syndrome, spinal cord injury, narcolepsy, syringomyelia, supranuclear palsy, and parkinson's disease

Dr. Hall: The table below displays NINDS funding levels supporting direct research on the specific disease listed. In addition, NINDS supports research that is related to these disorders, which has the potential to improve medical understanding, prevention, and treatment.

<u>Disease/Disorder</u>	<u>FY 1995</u>	<u>FY 1996</u>	<u>FY 1997</u>
	<u>Actual</u>	<u>Estimate</u>	<u>Estimate</u>
Gaucher's Disease	\$4,284,000	\$4,460,000	\$4,474,000
Duchenne muscular dystrophy	3,379,000	4,460,000	4,474,000
Alzheimer's Disease	14,291,000	14,859,000	15,128,000
Huntington's Disease	6,212,000	6,525,000	6,636,000
Multiple Sclerosis	42,991,000	45,158,000	46,072,000
Head injury	36,714,000	38,552,000	39,377,000
Stroke	71,988,000	75,588,000	77,119,000
Epilepsy	54,295,000	57,010,000	58,159,000
Batten Disease	2,069,000	2,172,000	2,221,000
Neurofibromatosis	2,354,000	2,480,000	2,532,000
Dystonia	2,061,000	3,163,000	2,199,000
Post-polio Syndrome	1,610,000	1,674,000	1,676,000
Spinal Cord Injury	14,515,000	15,246,000	15,555,000
Narcolepsy	2,673,000	2,758,000	2,795,000
Syringomyelia	361,000	378,000	383,000
Supranuclear Palsy	405,000	405,000	405,000
Parkinson's Disease	21,942,000	23,040,000	23,515,000

RESEARCH CENTERS

Mr. Porter: Identify the number and subject matter of Research centers supported in FY 96

Dr. Hall: The NINDS is planning to support 43 Research Centers in the FY 1996. The following table displays the anticipated breakdown by subject area. The NINDS also supports several program project grants, whose funding is contained in the research project grant mechanism, that provide clinical center type activities. Included are projects like the Huntington Disease Center Without Walls, the Epilepsy Research Center, the Clinical Stroke Research Center, the Center for Stroke Research, and the Research Center for AIDS Dementia.

NINDS RESEARCH CENTERS GRANTS

<u>Subject Area</u>	<u>Number</u>
Neurological Disorders of Early Life	3
Neurological Disorders of Aging	
Parkinson's Disease	1
Huntington's Disease	1
Alzheimer's Disease	1
Stroke	7
Epilepsy	5

Sleep Disorders	1
Demyelinating or Sclerosis Disorders	
Multiple Sclerosis	3
Amyotrophic Lateral Sclerosis	2
Neuromuscular Function, Normal & Abnormal	
Muscular Dystrophy	1
Other Neuromuscular Disorders	3
Neurological Infectious Disorders	2
Trauma and Injury	
Head and Brain Injury	9
Spinal Cord Injury	2
Neonatal Brain Injury	
Brain Tumors	2
Total	43

RESEARCH OF DR. GAJDUSEK

Mr. Porter: Did NINDS or any other component of NIH provide any funding for the research implicated in the sexual abuse case brought against Daniel Gajdusek, a NINDS intramural scientist?

Dr. Hall: The charges against Dr. Gajdusek do not implicate his research. They relate to allegations of personal misconduct unrelated to his duties as a senior intramural scientist. His research, which has been funded entirely by NINDS, has focused on a range of questions related to the identification of novel types of infectious diseases of the nervous system in humans and animals. Such infections are of interest because of the previously undescribed infectious proteins responsible for disease, as well as the public health concerns recently raised by one such disease--bovine spongiform encephalopathy, or mad cow disease. One such disease, kuru, has been observed only in remote populations of the South Pacific. Dr. Gajdusek's success in discovering the mode of transmission of kuru and his later work demonstrating transmission in laboratory animals were recognized by the awarding of the Nobel Prize in 1976.

HUMAN BRAIN PROJECT

Mr. Porter: Provide a table of the number of institutes and other Federal agencies involved in the Human Brain Project and their financial support.

Dr. Hall: FY 1995 funding for the Human Brain Project was as follows:

	<u>NIH Institutes</u>	<u>FY 1995 actual funding</u>
NIMH		\$3,166,154
NIA		173,380
NICHHD		513,764
NCI		---
NHLBI		---
NIDR		---
NINDS		390,809
NIDCD		172,786
NIDA		1,910,099
NIAAA		---
NLM		411,190
FIC		---
	Subtotal, NIH	\$6,738,182
	<u>Other Agencies</u>	
NASA		250,000
DOE		---
ONR/DOD		---
NSF		200,000
	Subtotal, Other Agencies	\$450,000
	TOTAL	\$7,188,182

STROKE RISK FACTORS AND HISPANIC HEALTH

Mr. Bonilla: Dr. Hall, it is my understanding that Hispanics have a higher risk of stroke. What are we learning about risk factors for and the impact of stroke, particularly as it relates to Hispanic health?

Dr. Hall: As we learn more about risk factors for stroke and its impact, we are finding similarities as well as differences among different populations. For example, atrial fibrillation is a heart condition that is an important treatable risk factor for stroke. Atrial fibrillation is found, though, only half as frequently in the Hispanic or Black population as it is in the white population.

Several points can be made about how stroke affects the Hispanic population. Stroke is the third leading cause of death overall in the U.S. In the Hispanic population stroke is the fifth leading cause of death. Also, the age-adjusted death rate for stroke in Hispanics is actually lower than for whites. There are a number of different types of stroke. One type of stroke is due to atherosclerosis, in other words, fatty deposits. The proportion of stroke that occurs when the atherosclerosis is extracranial--for example, in the carotid arteries leading to the brain--is similar among Blacks, Hispanics, and whites. However, intracranial atherosclerosis--within the blood vessels of the brain itself--is more frequent in Hispanics as well as Blacks, as compared to whites.

Diabetes is more prevalent in minority populations including Hispanic populations. Those with diabetes are more likely to have a stroke than those without. And so, diabetes is a specific risk factor for stroke in the Hispanic population. If someone has high sugar levels in their blood when stroke occurs--which may or may not be due to diabetes--that person is at greater risk for death following a stroke or for having another stroke. This is true of all people with hyperglycemia, no matter their ethnic background. We are looking at the role of diabetes as a risk factor for stroke. Of course, the time to intervene is before a stroke occurs. One of our grantees is coordinating an effort to determine the best way to educate the public about the importance of stroke risk factors, including diabetes. Other institutes at NIH are also interested in aspects of the relationship between diabetes and stroke.

In summary, we support a number of studies through which we seek to further identify and understand the ways in which stroke affects various populations. What we discover may help physicians in identifying high risk patients, provide information to people about ways they can reduce their risk of stroke, and may have therapeutic importance.

WOMEN AND STROKE

Mr. Bonilla: Dr. Hall, more than 87,000 American females die each year from stroke. More than 60 percent of fatal stroke victims are female. American's third leading cause of death, the leading cause of permanent disability and a major contributor to late-life dementia; stroke kills twice as many American females as breast cancer. What research efforts will benefit women with stroke?

Dr. Hall: More women die of stroke than men (3:2), but age-adjusted stroke death rates are higher for men until the +85 year-old age group. The reason for the higher number of women overall that are affected by stroke is that women live longer, and they have their strokes at an older age.

The NINDS supports a large stroke research program. One NINDS clinical study targeting women is the Women's Estrogen for Stroke Trial at Yale University. Women in this trial are post-menopausal, and have suffered a stroke warning sign or non-disabling stroke. The trial is randomized, double-blinded, and placebo controlled. Test subjects will receive estrogen therapy to evaluate whether it reduces the risk of recurrent stroke. More than six hundred women will be studied for up to five years. Data from this blinded study will not be available for several years.

It is important to note that the risk factors for stroke are largely the same for whites and minorities, and for males and females. Research advances in the area of stroke research and prevention will benefit all.

CEREBRAL PALSY

Mr. Stokes: Last year you reported a study that found a medication, given to mothers around the time of delivery, may prevent many cases of cerebral palsy. Do you have anything new to report on that study or others concerning cerebral palsy?

Dr. Hall: Cerebral palsy is a chronic disability. Faulty development of the brain or damage to motor areas of the brain results in the inability of affected children to control their muscle movements, so for example, they may have trouble walking or using their hands. Children who are born weighing no more than 3.3 pounds are 100 times more likely to have cerebral palsy than children born with normal birth weight.

The study you mentioned was a collaborative study involving an NINDS intramural scientist working with staff from the California Birth Defects Monitoring Program. What they found, by looking at medical records, was that very low birth weight babies (weighing no more than 3.3 pounds.) born to mothers who were given magnesium sulfate before delivery were less likely to have cerebral palsy than very low birth weight infants whose mothers had not received the medication. The magnesium sulfate was given to the mothers for other medical conditions; it was not given with the idea that cerebral palsy might be prevented.

This observation has spurred interest to further pursue this finding. The NINDS is planning feasibility studies regarding research needed to confirm this observation. These studies are being undertaken in collaboration with the NICHD. In addition, a randomized clinical trial of magnesium sulfate in preterm labor has begun at the University of Chicago with support by a private foundation. A number of groups are looking at existing data sets for magnesium effects. Also, a large retrospective case-control study in northern California has been proposed. The observation linking magnesium sulfate to the prevention of cerebral palsy is an example of how advances made with intramural support can stimulate new studies in the broader research community.

Mr. Stokes: How much is included in the budget for this initiative, and how does it compare to FY 1995?

Dr. Hall: In FY 1995, NINDS direct spending for research on cerebral palsy (CP) totaled \$2,783,000 which included \$388,000 in total costs for the intramural project which identified the association between the administration of magnesium sulfate to the mother and a lower incidence of CP in very low birth weight babies. The intramural project began in FY 1994 and looked at several aspects of cerebral palsy, not just the magnesium issue.

The extramural initiative to follow-up on this discovery began in FY 1996. In FY 1996, NINDS plans to spend about \$200,000 to plan for the extramural feasibility study under consideration. (The intramural project on CP will also continue in FY 1996.) In FY 1996, NINDS total direct spending for cerebral palsy is estimated at \$2,922,000.

STROKE

Mr Stokes: Stroke is America's No. 3 killer and the leading cause of permanent-disability. African-Americans have more than a 60 percent greater risk of death and disability from stroke than whites. Stroke is a major health problem for minority populations. The institute's progress in preventing and treating stroke shows the need to disseminate results of clinical trials but also to make the public more aware of stroke. What is the institute doing in this area, particularly any activities that may target specific populations?

Dr. Hall: As you know, we have developed a good system to disseminate information from clinical trials including press conferences, special information prepared for physicians, presentations at national and international meetings, and a number of materials specially prepared for the public. I would like to highlight some recent activities that extend our reach to inform the public.

First of all, the t-PA study would not have succeeded without an intensive public information campaign in those areas in which the study was being conducted to make people aware of the need for emergency treatment for stroke. Because the study was successful, we are now widening our effort. The trial involved a variety of health care settings including university medical centers, urban hospitals, and small community hospitals. All participated successfully and so provide us with models of how community care systems can respond to stroke. Further, we are working with a number of private groups to determine the next steps that should be taken to educate the public and the medical community about t-PA.

We also support an ongoing clinical trial to evaluate the use of ticlopidine compared to aspirin to prevent stroke in an African American population. This study will involve 1800 patients at 18 centers in the Chicago area. The study has the vigorous support of Church and community organizations. We expect that from the study the whole community will become more aware of the importance of stroke prevention and early treatment of high blood pressure and other risk factors.

In New York, we support two studies to look at stroke among Black, white, and Hispanic residents. Part of this study will examine risk factor modifications and their effect on outcome. What we learn from this study should help us to better understand stroke in these communities.

In addition, in 1995, all public education materials on stroke were posted on the World Wide Web which is one more avenue to use. Of course, we continue to update public education materials with new findings.

PARKINSON'S DISEASE

Mr. Stokes: When will the report from the 1995 Parkinson's conference be released, and how will the results be applied to the Institute's research activities?

Dr. Hall: The report has been completed and we are mailing copies to patient and professional groups and interested members of Congress. A copy is included for the record. NINDS has already launched several important initiatives in response to the conference.

In a collaborative effort with the National Center for Human Genome Research, intramural scientists are studying a group of families in which Parkinson's disease may be inherited. A program announcement, issued by NINDS on May 3, 1996, seeks applications from extramural scientists for investigations related to the genetics of Parkinson's disease.

The Institute has begun planning for a group of experts to refine criteria for diagnosing Parkinson's disease and for distinguishing it from neurodegenerative disorders with closely related symptoms. The goal of this effort is to improve current diagnosis and treatment and to better define future research directions.

Another program announcement, to be issued soon, will seek research applications in mechanisms of cell death and injury in neurodegenerative disorders. This research will provide the foundation for many important advances in Parkinson's disease research and lay the groundwork for the development of biomarkers and improved therapeutic measures.

The four Institutes sponsoring the conference (NINDS, NIA, NIMH, and NIEHS) have participated actively in the development of the program announcement on mechanisms of cell death and injury and have formed a Parkinson's Disease Coordinating Committee to share information and identify opportunities for additional collaborations. As noted above, the National Center for Human Genome Research is participating in genetic studies. Other ongoing NIH activities, notably the procedures for assigning grants for funding and for reviewing proposed extramural announcements, provide opportunities for these and other Institutes and Centers to contribute to progress in Parkinson's disease research.

In addition, the President's FY 1997 budget request includes additional funding for the "Biology of Brain Disorders." In an effort to begin this initiative as soon as possible,

the NIH Director has requested permission to transfer \$7.8 million from other accounts to increase funding for brain research in FY 1996. Within this total, \$2.3 million will be designated for research on new technologies for the study of Parkinson's disease.

The material for insertion follows:

[Clerk's Note: The requested material was deemed too lengthy for printing and has been retained in Committee files.]

CLINICAL TRIALS

Mr. Stokes: Minorities are disproportionately affected by many of the diseases which are under the purview of your Institute, can you bring the subcommittee up-to-date on the Institute's clinical trial aimed at addressing the most at risk populations? What has the institute done to ensure the enrollment of minorities in this major study?

Dr. Hall: Last year, NINDS began support for a major clinical trial to evaluate the use of ticlopidine compared to aspirin to prevent stroke in an African American population. Both medicines are considered "antiplatelet" medications, but they work by different mechanisms. The reason for this trial is that previous studies suggest that African-Americans may have a more favorable response to ticlopidine than the general population. This study will involve 1800 patients at 18 centers in the Chicago area. The study has the vigorous support of Church and community organizations which should facilitate enrollment of patients for the study. We expect that from the study the whole community will become more aware of the importance of stroke prevention and early treatment of high blood pressure and other risk factors.

This study is in addition to a number of ongoing studies supported by NINDS to better understand neurological disorders in minority populations. For example, studies are supported in New York to examine risk factors, incidence, and outcome from stroke in African-American, Hispanic, and white populations. Other studies relevant to minority health include studies of seizure disorders and head injury.

Mr. Stokes: What are some of your other most significant clinical trials, specifically what can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Hall: We are pleased to report findings or preliminary data from several clinical trials. A five year clinical trial involving more than 600 stroke patients at nine research centers across the country has shown that treatment with the clot-dissolving drug t-PA is an effective emergency treatment for acute ischemic stroke despite some risk from bleeding. When given within three hours of the onset of the most common type of stroke, t-PA increases the patient's chances for an excellent recovery by 30 percent. The t-PA trial is an important milestone, not only for this major treatment breakthrough, but also for the carefully crafted clinical and methodological approaches used to evaluate the outcomes of the trial which will guide future studies to determine the value of other stroke treatments.

Two trials are examining the effects of estrogen and androgen on the cognition and social behaviors of adolescent girls with Turner syndrome. This genetic disorder presents a unique opportunity to study the effects of hormones on brain function. Preliminary results indicate cognitive and behavioral deficits in the Turner syndrome

group; final results should assist in making medical decisions about hormone replacement therapies for girls with the syndrome.

In another trial, an important advance was achieved in preventing intraventricular hemorrhage (IVH) in very low birthweight infants by treating them with the drug indomethacin within 6-12 hours of birth. With such treatment, IVH is less likely to occur, and if it does, it is less severe and less likely to cause extensive brain damage. The study is now tracking indicators of cognitive and developmental outcome to assess the influence of indomethacin treatment in these areas.

Finally, an intramural study evaluated the toxicity of Tf-CRM107, a targeted protein toxin, and assessed antitumor activity in patients refractory to standard therapy for malignant brain tumors. Evidence of new or increased tumor necrosis and significant reduction in tumor size on MRI occurred in 60 percent of the evaluable patients. This trial suggests that Tf-CRM107 effects tumor responses without severe neurologic or systemic toxicity in patients with malignant brain tumors refractory to conventional therapy. This is the first demonstration of reproducible antitumor activity of immunotoxins for treatment of solid tumors in humans.

The Institute also initiated several new clinical trials in FY 1995. These trials include a study to evaluate the efficacy of ticlopidine hydrochloride and aspirin in the prevention of recurrent stroke, vascular death, and myocardial infarction in African-American patients with recent non-cardioembolic ischemic stroke; a trial to test whether intrastriatal grafts of fetal mesencephalon can safely improve and alter clinical progression of disability in patients with Parkinson's disease; and a trial to evaluate the role of aspirin in the prophylaxis of migraine in women as a substudy of the NIH women's health study.

In FY 1995, NINDS funded 64 clinical trials. Continuing trials include efforts to improve the outlook for infants with *neonatal seizures* through improved identification and diagnosis; a controlled clinical trial using pallidotomy versus best medical therapy in patients with intractable *Parkinson's disease*; a five-year study comparing the efficacy and safety of intravenous diazepam or lorazepam when administered in the field by paramedics to adult patients with *status epilepticus*; the Women's Estrogen for Stroke Trial (WEST) to determine whether unopposed estrogen therapy in post-menopausal women who have experienced a nondisabling stroke reduces the risk of death, recurrent stroke or other vascular events, or influences physical and/or cognitive functioning; and a randomized clinical trial that continues the work of the National Acute Spinal Cord Injury Study (NASCIS) to evaluate the effectiveness of pharmacologic therapy to improve permanent neurologic recovery after spinal cord injury.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for Clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Hall: In FY 1997 Clinical trials will continue to play an invaluable role in the NINDS mission. The following table will show the relationship between FY 1997, FY 1996, FY 1995, and FY 1994's funding level for Clinical Trials by the NINDS:

<u>Fiscal Year</u>	<u>Amount of Clinical Trials</u>
FY 1997 Estimate	\$39,685,000
FY 1996 Estimate	39,037,000
FY 1995 Actual	37,180,000
FY 1994 Actual	40,125,000

Mr. Stokes: What is the institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Hall: It is NIH policy that minorities and women be included in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study. The composition of the proposed study population must be described in research applications in terms of gender and racial or ethnic groups, and special emphasis is placed on the need for inclusion of minorities and women in studies of diseases or disorders that disproportionately affect them. The NIH also has a gender/minority tracking system used to monitor inclusion for all NIH-defined Phase III clinical trials, as well as for clinical research studies that involve contact, interaction, or intervention with human subjects.

Minority populations are particularly affected by some of the diseases and disorders within the mission of NINDS, and the Institute has several clinical trials specifically designed to enroll minority populations or women. For example, African-Americans experience stroke at a higher rate, have more severe strokes, and are twice as likely to die from a stroke as white Americans. NINDS is supporting the African-American antiplatelet stroke prevention clinical trial, a major new trial funded in FY 1995. An aspect of this study is to educate the community about the importance of stroke prevention and early treatment of high blood pressure and other modifiable risk factors. The Institute continues to support a study which is investigating, in African-Americans, Hispanics, and Caucasians, the risks of stroke recurrence, myocardial infarction and death in 30-day survivors of cerebral infarction, as well as a study at the University of Cincinnati to provide a comprehensive comparison of stroke incidence rates between African-Americans and Caucasians in a metropolitan population. An understanding of the role of individual risk factors and their interactions with ethnicity may lead to more selective secondary prevention strategies. NINDS-supported investigators are also conducting a case control study of stroke in

young women aged 15 to 45 years. A main focus of the study will be the use of oral contraceptives and the incidence of migraine headache as risk factors for stroke in a designated biracial population.

The prevalence of migraine is approximately 6% among men and 18 % among women. In the general population, migraine prevalence increases as income decreases. From a health care delivery and cost perspective, women from lower income households have a greater risk of experiencing migraines, and are more likely than other groups to use emergency care services for treatment. In FY 1995, the NINDS awarded a multi-year, multi-component grant that establishes a Headache Clinical Research Center at the Henry Ford Health Sciences Center in Detroit, Michigan. This major, new initiative provides the opportunity for focused and longitudinal research studies of headache, with the specific goal of investigating the causes, mechanisms, and consequences of migraine. The grant includes specialized recruitment support to ensure the participation of women and minorities.

In the area of epilepsy, a five-year study supported by NINDS is comparing the safety and efficacy of intravenous diazepam or lorazepam versus placebo when administered in the field by paramedics to adult patients in status epilepticus (SE). SE is more prevalent among inner city populations. The Institute is supporting a study that will examine the developmental impact of complex partial seizure disorder (CPSD) on children's thought processes. Participating in the study will be an equal number of boys and girls of Caucasian, African -American, Asian and Hispanic origin.

Finally, a large program project at Duke University Medical Center includes genetic linkage studies of neurogenetic disorders. One component of the project is studying the genetics of Native American myopathy, a syndrome consisting of congenital myopathy, cleft palate, malignant hyperthermia, and skeletal anomalies.

GENE THERAPY

Mr. Stokes: Does the Institute place too much emphasis on genetics, given the recent assessment of the gene therapy panel that gene therapy is being "oversold?"

Dr. Hall: The gene therapy panel stated that the results of gene therapy have been oversold, giving the impression that gene therapy is more developed than it actually is. The panel recommended emphasizing genetic research on basic biological questions to understand disease pathogenesis and to develop animal models for human diseases. That is the current emphasis of NINDS funding of genetic research. In FY 95 NINDS funded research directed toward developing gene therapy accounted for only \$2.35 million, while genetic research generally was more than \$54 million.

Genetic discoveries can provide direct benefits for health care before gene therapy becomes feasible. Diagnostic tests for several neurological diseases and screening tests for carriers of disease genes are rapidly becoming practical; several tests are already commercially available. Diagnosis of inherited nervous system disorders can be difficult because there are hundreds of neurologic diseases and many are rare. Accurate diagnosis is often crucial for treatment decisions. Carrier detection also can be very helpful to families, as was dramatically demonstrated in the recent ABC television documentary about ataxia telangiectasia. Obviously any genetic testing requires expert genetic counseling and adherence to ethical guidelines. The NIH-DOE task force on genetic testing has issued its Interim Principles and will develop final recommendations with public input. We are carefully following their lead.

In addition to the direct effects of genetic discoveries on patient care, genetics provides powerful tools for understanding what causes neurological diseases. The primary defects triggering many neurologic diseases are unknown. Genetic discoveries have already yielded important clues in amyotrophic lateral sclerosis (Lou Gehrig's disease), Alzheimer's disease, Duchenne muscular dystrophy, Huntington's disease, myotonic dystrophy, and several hereditary nerve diseases, to name just a few. Many common non-inherited neurological diseases occur in a less common, strongly inherited form, for example Alzheimer's and amyotrophic lateral sclerosis. In these two and many other examples genetic research into the causes of a less common familial form of a disease can dramatically advance understanding of the more common non-hereditary forms of the same disease. NINDS is now pursuing this strategy for Parkinson's disease in cooperation with the Human Genome Center. Genetic engineering is also the best source of animal models for neurologic diseases that are crucial for understanding disease processes and for developing new therapies.

Genetic research, apart from gene therapy, is central to progress in all areas of neurobiology and neurologic disease. I believe NINDS' current investment in genetic research is appropriate and in keeping with the spirit of the gene therapy panel recommendations. We should also not forget that the panel, while warning that progress in gene therapy may have been oversold, also stressed that gene therapy "offers extraordinary potential, in the long term, for the management and correction of human disease."

Mr. Stokes: How critical is gene therapy research to furthering advances in areas of research which are under the purview of your Institute? What diseases and disorders would benefit from enhanced research in this area?

Dr. Hall: More than one third of all genetic diseases affect the nervous system. Hundreds of inherited neurological disorders have been recognized. Among these are diseases that strike children, such as neurofibromatosis, muscular dystrophy, Batten disease and Friedreich's ataxia, and diseases that have devastating impact on adults, such as Huntington's disease and familial Alzheimer's disease. When gene therapy becomes

practical, it may offer hope for some of these disorders. Furthermore, gene therapy holds promise for some non-genetic disorders, such as brain tumors, for which few, if any, effective therapies are presently available. However, as the recent gene therapy panel reported, significant advances in genetic technology will be necessary before gene therapy becomes feasible for most genetic diseases. Germ-line gene therapy in particular, which might be necessary to "treat" childhood and other inherited diseases, is a long way off.

As the gene therapy panel emphasized, genetic research is crucial for understanding the causes of disease and for developing animal models. Genetic research is central to progress in understanding the normal nervous system and its disorders. Experience so far clearly shows that finding the genes responsible for inherited forms of neurologic diseases can be crucial for understanding non-inherited disorders as well. Finding disease genes can also lead to diagnostic aids and screens for carriers of defective genes long before gene therapy becomes practical. For these reasons, NINDS' investment in gene therapy is cautiously directed where present understanding is most likely to allow progress, but our broader commitment to genetic research about neurologic diseases is very strong.

AUTISM

Mr. Stokes: The Committee has encouraged trans-NIH support for research on autism. How will your institute be pursuing the recommendations from the conference held last year?

Dr. Hall: The NINDS was very pleased to cosponsor this conference and is committed to continued support of research in autism and to working with other Institutes on this disorder. Summaries from the conference were to be published in April 1996. The NINDS is planning a program announcement which may be cosponsored with other Institutes incorporating research recommendations from the conference.

The current portfolio of NINDS research already actively addresses some of the recommendations highlighted by the conference. Further, NINDS has sought innovative new approaches to some of the fundamental research issues in autism. One question has been to identify the brain regions that are affected in autism. Results to date have been variable; some studies have suggested that individuals with autism may have reduced size of certain parts of the brain while other studies have shown brain overgrowth. NINDS is supporting new research to clarify the issue of relating brain anatomy to autism. NINDS also supports several studies with patients to look at attention, language, and brain development.

Mr. Stokes: Dr. Hall, what are some examples of advances in the prevention of neurological conditions, how far have we come and what are some of the major barriers and/or challenges ahead?

Dr. Hall: There have been several recent findings relating to the prevention of neurodevelopmental disorders:

the observation that administration of magnesium sulfate to mothers in labor may reduce the risk of cerebral palsy in low-birthweight babies,
 an excessive intake of vitamin A through supplements in pregnancy may cause cranial-neural-crest tissue birth defects (e.g., craniofacial defects such as oral clefts, abnormalities of the ears, eyes and nose; also, microcephaly, hydrocephaly)
 insufficient maternal intake of the vitamin folic acid during the earliest weeks of pregnancy may place the newborn infant at risk for neural tube defects such as spina bifida. After several years of gathering and analyzing findings from studies, the FDA has recommended that grain products be fortified with folic acid to reduce the occurrence of these conditions.

These findings are especially important because they all represent relatively simple and inexpensive ways to prevent common, devastating conditions.

We are particularly encouraged by the progress that has been made in the prevention of stroke. Thanks in part to the educational efforts of our colleagues in NHLBI, stroke deaths have declined by 50 percent in the United States. Elderly people with atrial fibrillation, a common disturbance of heartbeat, can significantly reduce their risk of stroke by taking aspirin or warfarin to prevent the formation of blood clots in the vessels that supply the brain. Two surgical trials have shown the benefits of the removal of blockages in the carotid artery for specific populations at risk. Another ongoing trial is examining the role of estrogen in preventing stroke in postmenopausal women.

Many neurological diseases are related to, or caused by defective genes, a phenomenon that presents challenges requiring novel approaches to prevention. As we learn more about how certain genes act to alter the normal functions of the nervous system, we hope to be able to devise preventive intervention strategies for those at high risk.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: For the diseases and disorders that are under the purview of your Institute, where do we stand today with respect to closing the gap in minority health, specifically what progress do you have to report to the subcommittee this year? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Hall: Minority populations are particularly affected by many of the diseases and disorders within the mission of NINDS; therefore, we currently support numerous studies addressing issues of concern to minority Americans. We are continuing collaborative efforts regarding minority health and are currently conducting several studies in the areas of epilepsy, head injury, stroke, neuro-AIDS, diabetic neuropathy, developmental disorders, genetics, and neurological aspects of chemical use and dependency. Some examples include:

- a study of African-American antiplatelet stroke prevention
- a study of the effect of stroke risk factors, and the 1-4 year stroke prognosis
- a study to provide a comprehensive comparison of stroke incidence rates between African Americans and Whites
- a study to understand the etiology of stroke in all segments of our society
genetic linkage studies including studying the genetics of Native American myopathy
- a study of the effects of neonatal cocaine intoxication and withdrawal.
- a study of the use of oral contraceptives and migraine headaches as risk factors for stroke
- a study examining the developmental impact of Complex Partial Seizure Disorder on children's thought processes
- a study to determine the minimal threshold of closed head injury severity sustained by children and adolescents eight to 16 years of age that is necessary to produce significant consequences during the first year post injury

Recent results from a trial in stroke, which is more prevalent in several minority groups, have significant potential for closing the gap in minority health. NINDS-supported investigators designed an emergency treatment program to work within three hours of the onset of the most common type of stroke, that is due to a blood clot blocking a brain artery. In the clinical trial, the drug, t-PA, was administered within three hours of a stroke to dissolve the offending clot and restore blood flow. The results from the clinical trial show that t-PA increases one's chances for an excellent recovery by 30 percent when given within three hours.

Another example is one in which NINDS investigators found that administering magnesium sulfate shortly before and during preterm birth was associated with marked reduction in cerebral palsy. Children born very prematurely are at high risk of cerebral palsy, which is more common in minorities. In this study the apparent protective effect was noted in infants born to women with pregnancy-induced hypertension, to whom it was given to prevent convulsions, and also in infants whose mothers were not hypertensive, who were given magnesium in an attempt to halt preterm labor. This is the first therapeutic approach to show apparent prevention of motor disability in very premature infants.

NEUROLOGICAL DISEASES IN WOMEN

Mr. Stokes: Dr. Hall, are there any neurological diseases that are seen mostly in women? What research is your Institute funding on these diseases? Which of these are collaborative efforts with the Office of Women's Research initiative?

Dr. Hall: Several neurological diseases are seen more often in women: multiple sclerosis (MS), two times more common in women; migraine headache, three times more common in women; systemic lupus erythematosus (SLE), ten times more prevalent in women; and myasthenia gravis (MG), three times more common in women. More women than men have strokes because stroke is mainly a disorder of the elderly, and women tend to live longer; also, women have strokes at a later age than men.

The NINDS maintains a large portfolio of research grants related to multiple sclerosis, which is thought to be an autoimmune disease. It is not clearly understood why autoimmune diseases strike women more often than men. Studies specific to women include grants that are examining immune status in pregnant and post-partum multiple sclerosis patients, and animal studies exploring the role of gender in the development of autoimmune diseases. Investigations into myasthenia gravis and systemic lupus erythematosus, also autoimmune disorders, are in progress.

In response to a program announcement entitled "Neurological Basis of Recurrent Headache, Especially Migraine," in 1995 the NINDS awarded a multi-year grant to establish a headache center at the Henry Ford Health Sciences Center in Detroit. There is specialized support to ensure the recruitment and participation of women and minorities.

Also supported by NINDS is a grant entitled "Low Dose Aspirin in the Prophylaxis of Migraine Headache." It will be looking specifically at women, using a subproject of an NIH women's health study.

NINDS has received supplemental funding from the NIH Office for Research on Women's Health for selected active grants that target conditions, diseases or disorders related to women. Examples of awards include additional funding for grants studying maternal and child health in women with inborn errors of metabolism, and the study of anti-epileptic drugs in pregnancy using primate animal models.

In the area of stroke in women, the NINDS is funding a trial to evaluate the role of estrogen in stroke prevention.

COST OF STROKE TO THE NATION

Mr Stokes: How much does stroke cost this nation and how much is being spent on Institute-supported research? How much stroke research will the president's budget

allow you to support in FY 1997? In your professional judgment, how much is needed to support promising research opportunities in stroke research?

Dr. Hall: The latest estimate puts the cost of stroke in excess of \$30 billion annually. (Agency for Health Care Policy and Research Patient Outcomes Research Team, September, 1994.) Spending by NINDS for stroke research was \$71,988,000 in FY 1995; \$75,588,000 estimated in FY 1996; and an estimated \$77,119,000 under the President's budget for FY 1997. At the professional judgment level, funding for stroke research by NINDS in FY 97 would be \$83,289,000.

GENETIC PREDISPOSITION FOR NEUROLOGIC DISORDERS

Mr. Stokes: What is the association between genetic predisposition and the diseases and disorders under the purview of your Institute?

Dr. Hall: The brain is the most complicated organ of the body. About half of the 100,000 human genes probably play an important role in the nervous system. Not surprisingly, more than a third of all inherited diseases affect the nervous system, so hundreds of genetic disorders of the nervous system have been recognized.

The best understood genetic disorders of the nervous system are directly caused by mutations in single genes, for example Huntington's disease and ataxia telangiectasia. As genetic technology advances, how single genes and complex interactions of genes may predispose us to neurological diseases, rather than directly causing disorders, is beginning to become apparent. Mutations in any of three different genes can directly cause the inherited form of Alzheimer's disease, for example, and the form of a fourth gene we all carry determines our likelihood of developing the non-inherited form of Alzheimer's. Complex interactions among genes probably influence our predilection for most neurologic disorders. Understanding these genetic factors is likely to become important in treating and preventing neurologic diseases in the future.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your Institute?

Dr. Hall: NINDS continues to participate in NIH-wide programs geared toward recruiting and retaining minorities in the biomedical sciences including the Minority Access to Research Careers (MARC) and the Minority Biomedical Research Support Program (MBRS). In addition, the Institute has recently introduced five new programs.

With funding from the Office of Research on Minority Health, NINDS has awarded a cooperative agreement to the Morehouse School of Medicine for a Developmental Neuroscience Research Program. The Morehouse School of Medicine (MSM) is a part of the Atlanta University Center, a consortium of schools that train one of the largest pools of underrepresented minority students in the United States. The Developmental Neuroscience program is intended to establish a research infrastructure and to develop neuroscience expertise to support studies on the functional organization and development of the nervous system. The current research efforts are focused on the molecular biology and physiology of circadian rhythm generation, signal transduction and modulation in the basal ganglia, neurotoxicity associated with Human Immunodeficiency Virus (HIV) infection, and the biochemical correlates of animal behavior. One important aspect of the program is that it will promote substantial research collaborations between investigators at MSM and other well-established NINDS grantees at other institutions. The long-term goal of the cooperative agreement is to support a neuroscience research and training program that will develop independent investigators who will be competitive for funding at the national level. The Developmental Neuroscience Research Program will be officially dedicated in May, 1996.

The new Ernest Everett Just Faculty Research Career Development Award provides support to enable the recipient to develop his or her research skills, with the ultimate objective of making the recipient more competitive for traditional NIH grant support. The award is intended to further career development of faculty members at historically Black colleges and universities as neuroscientists.

Another new program, the Collaborative Neurological Sciences Award, seeks to encourage collaborative investigations between scientists at predominantly minority institutions and grantees from research-intensive institutions who have NIH support to conduct neuroscience research. The award is intended to develop and expand neurological training opportunities among the participating institutions.

Training grant program directors who use a slot (pre doc or post doc) in a budget period for the recruitment of an underrepresented minority are provided with sufficient funds for the appointment of an additional trainee, who may or may not be a minority individual. This means that a principal investigator can exceed the 4/3 cap. However, overall budget limits on training still apply.

Another new program in FY 1995 is the Predoctoral Fellowship for Minorities. This program provides an incentive for underrepresented minorities to obtain research training in the nation's best graduate programs. These awards are conditional upon acceptance into an approved doctoral degree (Ph.D.) or combined-degree (M.D.-Ph.D.) program in the neurological sciences.

These new efforts are in addition to ongoing efforts by NINDS to award Minority Supplements, made as supplemental funds to active research grants for supporting underrepresented minority scientists and students, and the NINDS Summer Program in the Neurological Sciences. The Summer Program offers high school, undergraduate, graduate, and medical school students the opportunity to conduct hands-on research with leading neuroscientists in the NINDS Intramural program. There are currently more than 700 "graduates" of the program (approximately 135 minorities) who are now training for careers in biomedical research or academic medicine at such prestigious institutions as Harvard, Stanford, and Johns Hopkins.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 97 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Hall: Each week the NINDS receives thousands of letters and phone inquiries from the general public, the media, Congressional staffs, health-care providers, and scientists on the most common neurological disorders (e.g., stroke, Parkinson's disease, epilepsy) as well as on less common neurological disorders that affect as many as 150 million Americans each year. One of the most critical components of our public education efforts involves providing prompt, accurate answers to questions from patients, parents, and relatives dealing with an unexpected and serious health problem often without treatment or cure. Inquiries are answered with fact sheets, brochures, standard and custom letters developed by Institute staff as well as with phone calls, and, increasingly, referrals to the NINDS Home Page on the World Wide Web. This Web site has been established and is kept up to date by staff so that it contains many of our printed documents, as well as a full listing of private health organizations that can assist patients with many of the day-to-day problems they face, such as obtaining physician referrals and financial aid.

In keeping with the need to do more with less, NINDS public education staff routinely work with hundreds of voluntary health organizations who serve as a gateway to the public, and with a growing number of private educational groups which market vital health information to citizens. One such education effort is the NINDS participation in a new project called *Libraries as Gateways*, organized by the National Health Information Center. *Gateways* is a joint effort on the part of Federal health information centers to help community libraries become resources for consumer health information. NINDS has provided many of its health education publications for this project, which has the potential to serve consumers in small communities with limited access to health information. A similar project in which the Institute participates is

HealthTouch, a private health information computer system found in thousands of pharmacies around the country. While visiting their pharmacies, consumers are able to access databases containing health information provided by national health organizations, including the NINDS. These consumers can print out short leaflets describing the topic of interest to them.

Stroke education is a particularly high priority for NINDS. For a number of years, the NINDS has spearheaded an outreach program to convey important stroke prevention information to the public. In 1995, NINDS scientists made a breakthrough discovery that will forever change the way that stroke is treated in this country. Staff are now involved in developing plans for a public and professional education campaign to realize the benefits of our research results. This is no small challenge: our research shows that in order to be beneficial, treatment must be initiated within 3 hours of the initial symptoms of a stroke. Our initial efforts, therefore, will be to get individual groups of health care professionals to rethink the way they respond to stroke patients and to develop their own standards and guidelines for emergency treatment of stroke. This means, not just the neurologists, but the internists, the emergency medical specialists, radiologists, nurses, emergency medical technicians, and perhaps more importantly, the hospital and HMO administrators.

In FY 1994, the NINDS spent approximately \$702,000 on outreach and public education programs. In FY 1995, this increased to \$1,126,000 and has remained relatively constant since that point (FY 1996 estimate: \$1,154,000; FY 1997 estimate: \$1,154,000).

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account; is this the case in your Institute? If so, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are you hurting the most?

Dr. Hall: Yes, these programs are funded through research management and support.

Demands on the Institute's public information staff time and resources continue to increase as the expanding reputation and visibility of the NIH, coupled with a more informed constituency, increase the public's access to us. This is a trend we have worked toward and do not wish to discourage. Although we continue to respond to public demand for health information, increased cost of personnel and reductions in RMS funding levels will result in cuts in some of our most important communications mechanisms. For example, flat budgets, coupled with the increased costs of printing and reproduction, mean we will publish fewer health information brochures and fact sheets. This will, in turn, affect the amount of information we are able to provide to those who call and write for information, particularly because so many of our inquiries deal with rare disorders. To provide useful information on these disorders, staff must spend time

searching the published literature, contacting researchers who may have up-to-date information, and photocopying relevant information. Budget restrictions will necessitate some reductions in these efforts to answer questions from the public. Finally, funding limitations could possibly cause Institute staff to delay other outreach initiatives, for example, educational programs aimed at improving science literacy among America's school-aged children and programs intended to educate the public, especially teens, about head injuries.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Hall: There are several collaborative efforts underway between NINDS and the Office of Research on Minority Health (ORMH). With funding from ORMH, and with substantial involvement of three professional NINDS staff members, NINDS has awarded a cooperative agreement to the Morehouse School of Medicine for a Developmental Neuroscience Center. The program supports research on the development and function of the nervous system and promotes substantial research collaborations between investigators at Morehouse School of Medicine and NINDS grantees at other institutions. The purpose of the cooperative agreement is to assist Morehouse in developing a competitive neuroscience research program and also serve as a model for other historically Black colleges and universities (HBCUs) in developing competitive biomedical research programs in neuroscience or other fields.

In addition, NINDS and ORMH collaborative efforts include funding by the ORMH for Clinical Investigator Development Awards (CIDAs) and minority research supplements. ORMH funding enables a greater number of individuals to be supported.

Projects in NINDS that were totally funded by the Office of Research on Minority Health in FY 1995 include the following:

FY 95 RESEARCH SUPPLEMENTS FUNDED BY ORMH

Title and Institution	Principal Investigator	Period of Performance	Funding
Molecular Basis Of Axolemmal-Glial Interaction Virginia Commonwealth University	De Vries, George H	04-01-95 to 02-29-96	\$10,559
Neurogenetics Of Membrane Excitability University Of Wisconsin Madison	Ganetzky, Barry S	07-01-95 to 06-30-96	\$39,956
Pathogenesis Of Oligosaccharide Disorders Michigan State University	Jones, Margaret Z	07-01-94 to 06-30-95	\$,617
MacRomolecules Involved In Synapse Formation University Of Maryland Balt Prof School	Bloch, Robert J	04-01-95 to 03-31-96	\$63,075
Peptidergic Neurons In The Spinal Cord University Of Minnesota Twin Cities	Seybold, Virginia S	07-01-94 to 06-30-95	\$1,378
Permeability Control Of Acetylcholine Receptor Harvard University	Cohen, Jonathan B	12-01-94 to 11-30-95	\$6,342
Gaba Mediated Anticonvulsant Actions And Basal Ganglia Georgetown University	Gale, Karen N	07-01-95 to 06-30-96	\$6,440
Fluctuations In Ionic Current Through Membrane Channels Yale University	Sigworth, Frederick J	12-01-94 to 11-30-95	\$4,229
Interactions Of Neural Cams With Extracellular Proteins New York University	Grumet, Martin H	04-01-95 to 03-31-96	\$53,652
Neurobehavioral Outcome Of Head Injury University Of Maryland Balt Prof School	Levin, Harvey S	07-01-95 to 05-31-96	\$52,621
Modulation Of Neuronal Acetylcholine Receptors Columbia University New York	Role, Lorna W	07-01-95 to 05-31-96	\$52,540

Structural Correlates Of Cortical Information Processing Henry M. Jackson Fdn For The Adv Mil/Med	Juliano, Sharon L	04-01-95 to 03-31-96	\$8,837
Regulation Of Membrane Excitability Colorado State University	Beam, Kurt G	05-01-95 to 04-30-96	\$21,934
Transmission Of Respiratory Drive To Phrenic Motoneurons University Of California Los Angeles	Feldman, Jack L	04-01-94 to 03-31-95	\$8,174
Static And Dynamic Organization Of Motor Cortex Brown University	Donoghue, John P	07-01-95 to 06-30-96	\$26,321
Hormonal Modulation Of A Communication Signal University Of Texas Austin	Zakon, Harold H	12-01-94 to 11-30-95	\$50,811
Modulation Of Muscarinic Responses By Inositol Lipids University Of Minnesota Twin Cities	El-Fakahany, Esam E	02-01-95 to 01-31-96	\$17,951
Amines, Peptides And Aspects Of Behavior Harvard University	Kravitz, Edward A	07-01-94 to 06-30-95	\$7,119
Neurobehavioral Sequelae--Mild Brain Injury In Children University Of California Los Angeles	Asarnow, Robert F	04-08-94 to 03-31-95	\$31,268
Neurobehavioral Outcome Of ECMO Neonates At Age 5 Children's National Medical Center	Glass, Penny	04-01-94 to 03-31-96	\$19,413
Sensory Integration In Somatosensory Motor Cortex Henry M. Jackson Fdn For The Adv Mil/Med	Porter, Linda L	12-01-94 to 11-30-95	\$5,100
Normal Voltage Gated Potassium Channels University Of Washington	Tempel, Bruce L	12-01-94 to 11-30-95	\$59,579

Mechanisms Of Lipase Activation In Alzheimers Disease Ohio State University	Horrocks, Lloyd A	04-01-95 to 03-31-96	\$12,814
Affinity Labels For Inositol Polyphosphate Receptors State University New York Stony Brook	Prestwich, Glenn D	04-01-95 to 02-29-96	\$33,989
Excitatory Synaptic Transmission In Neostriatum Vanderbilt University	Lovinger, David M	12-01-94 t 11-30-95	\$53,492
Excitatory Amino Acid Transport University Of Montana	Bridges, Richard J	12-01-94 to 11-30-95	\$5,290
Neuronal Cell Determination In The PNS Case Western Reserve University	Hall, Alison K	04-01-95 to 03-31-96	\$6,795
Inhibition And Deinhhibition Of Neurite Outgrowth University Of Florida	Muir, David F	12-01-94 to 11-30-95	\$8,345
Endogenous Antiopiate Analgesia Systems University Of Colorado At Boulder	Watkins, Linda M	09-29-95 to 09-28-96	\$36,291
Cognition And Cerebrovascular Disease Boston University	Moss, Mark B	12-01-94 to 11-30-95	\$66,804
Overexpression Of Nerve Growth Factor University Of Kentucky	Davis, Brian M	05-01-95 to 04-30-96	\$23,840
Tubulin Transport In Axon Regeneration Johns Hopkins University	Hoffman, Paul N	07-01-95 to 12-31-95	\$24,926
Transthyretin And HIV-Related Neurologic Disease Johns Hopkins University	Royal, Walter, III	04-01-95 to 02-29-96	\$2,735
Cell Adhesion Molecules In Myelination Mount Sinai School Of Medicine	Lazzarini, Robert A	05-01-95 to 04-30-96	\$40,954

Paraplegic Walking Made Practical With FNS And Orthoses Case Western Reserve University	Marsolais, Ernest B	09-01-94 to 08-31-95	\$29,387
In Vivo Studies Of The Epileptic Hippocampus University Of California Los Angeles	Engel, Jerome, Jr	08-01-94 to 07-31-95	\$7,016
Gene Delivery To The CNS To Modulate Epilepsy Georgetown University	Rabkin, Samuel D	08-01-95 to 07-31-96	\$3,220
Oxidative Activation Of PKC During Induction Of LTP University Of Pittsburgh At Pittsburgh	Klann, Eric	05-01-95 to 02-29-96	\$28,996
Molecular Mechanisms Of HIV Neuropathogenesis University Of Nebraska Medical Center	Gendelman, Howard E	05-01-95 to 04-30-96	\$7,514
Strategies To Enhance Adenoviral Gene Transfer To CNS University Of Iowa	Davidson, Beverly L	02-14-95 to 01-31-96	\$13,052

FY 95 COOPERATIVE AGREEMENT FUNDED BY ORMH

Title and Institution	Principal Investigator	Period of Performance	Funding
Developmental Neuroscience Research Grant Morehouse School Of Medicine	MacLeish, Peter R	09-30-95 to 08-31-96	\$1,000,000

FY 95 CIDA's FUNDED BY ORMH

Title and Institution	Principal Investigator	Period of Performance	Funding

Type I Adenylyl Cyclase Promoter University Of Washington	Villacres, Enrique C	09-01-95 to 08-31-96	\$87,480
Physical Conversion Of PRPC Into PRPSC University Of California San Francisco	Butler, Darel A	07-01-95 to 06-30-96	\$86,400

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Hall: In FY 1995, some projects were co-funded with the ORMH. Co-funding by the ORMH enables a greater number of investigators to be supported. The following projects were co-funded by NINDS and ORMH in FY 1995.

FY 95 RESEARCH SUPPLEMENTS CO-FUNDED BY NINDS AND ORMH

Title and Institution	Principal Investigator	Period of Performance	Funding
Coupled Fluxes of Mg++, Na+, K+ & Cl-In Excitable Cells Finch Univ of Hlth Sci/Chicago Med Sch	Rasgado-Flores, Hector F.	08-01-95 to 07-31-96	\$167,191(NS) \$30,515(OR)
Molecular Basis Of Periodic Paralysis Unviersity of Pittsburg at Pittsburgh	Hoffman, Eric P.	05-01-95 to 03-31-96	\$15,109(OR) \$1,416(NS)

FY 95 CIDAs CO-FUNDED BY NINDS AND ORMH

Title and Institution	Principal Investigator	Period of Performance	Funding
G Proteins In Pituitary Adenomas Emory University	Oyesiku, Nelson M.	09-30-05 to 09-29-96	\$90,120(OR) \$60(NS)

NATIONAL INSTITUTE OF MENTAL HEALTH

INTRAMURAL RESEARCH PROGRAM AT ST. ELIZABETHS

Mr. Porter: Do you think that the NIMH intramural research program at St. Elizabeths Hospital in Washington, D.C. should be closed or shifted to the NIH campus?

Dr. Hyman: The NIMH Neuroscience Center at St. Elizabeths and the NIMH Neuropsychiatric Research Hospital are located on Federal property on the St. Elizabeths campus and have long provided both laboratory space and inpatient clinical facilities in support of intramural clinical research, most notably an outstanding intramural program of schizophrenia research. The psychiatric research hospital has provided a cost-effective setting for the longer-term research hospitalizations of individuals participating in schizophrenia research. Evaluation will continue of whether St. Elizabeths is the most appropriate setting in which to conduct NIMH intramural clinical research.

BRAIN IMAGING

Mr. Porter: You have stated that you feel the use of brain imaging in neuroscience research needs to be reviewed more carefully. How do you intend to increase the scrutiny given to the use of brain imaging through the peer review process?

Dr. Hyman: Brain imaging in neuroscience research represents our best current opportunity to make the leap between basic animal research and clinical research. Neuroimaging permits us to see the living, thinking, feeling human brain at work. My concern in reviewing this type of research is that imaging scientists make use of the best available knowledge of brain circuits and of the knowledge of brain activation processes discovered by basic behavioral scientists. In short, excellent neuroimaging research is inherently interdisciplinary, requiring not only clinicians and imaging physicists but also basic integrative and behavioral neuroscientists. The proposed integration of the NIMH peer review process into the Division of Research Grants at NIH provides us with a wonderful opportunity to improve the review of neuroimaging proposals by ensuring adequate interdisciplinary representation on review panels. In addition, I already have instructed our program staff to be aware of the need for appropriate interdisciplinary inputs into neuroimaging research.

NIMH PEER REVIEW

Mr. Porter: As part of the consolidation of NIMH into NIH after its transfer from SAMHSA, the NIMH peer review system is due to be merged with the NIH system this year. Apparently some in the outside community are concerned that the NIH peer review process won't treat their grants fairly. Is this a reasonable fear, since NIMH supports much the same type of neuroscience research as the Neurology and Aging Institutes?

Dr. Hyman: The NIH and the NIMH are both committed to providing fair and rigorous scientific review for all grant applications. This year the congressional injunction against merger of the review committees of the former ADAMHA institutes, NIMH, NIDA and NIAAA, will expire. NIMH research, while having some areas of interest in common with other NIH institutes, requires more expertise in the highly complex areas of behavior and cognition. However, the NIMH believes that its scientists can receive a fair review within the NIH review structure because the appropriate scientific expertise will be moved from NIMH committees to new or reconstituted NIH committees, as necessary, to achieve this goal. We hope to answer fears within the scientific community by increasing our levels of communication throughout the merger negotiations and functional implementation.

CHILDHOOD MENTAL DISORDERS

Mr. Porter: Research on childhood mental disorders is a priority for your Institute. Would you please describe what NIMH is doing in this area and your plans for the coming year?

Dr. Hyman: NIMH has made extensive efforts over the last several years to expand the pediatric mental illness treatment research portfolio. This expansion was undertaken because of significant difficulties encountered in developing psychopharmacologic and psychosocial treatment research in children and adolescents. Despite a lack of pediatric treatment research data, psychoactive medications in children are widely used "off-label." To encourage more research in this area, NIMH has hosted a number of consultative meetings with investigators, community members, and the FDA. As a result of these programmatic efforts, the number of psychopharmacologic grants has nearly doubled in the last few years, and the next few years are likely to witness substantial further progress in this area. In this year we plan to expand current psychopharmacologic research through a series of supplements to researchers who have not focused on children, in order to enlist them in this effort. Also, we expect to let several competitive contracts to investigators to conduct psychopharmacologic research in high public need areas.

To encourage similar progress in the area of psychosocial treatments, NIMH staff have developed a consortium of psychosocial treatment investigators, designed to encourage and train new investigators in psychosocial treatment research, and to prepare them to apply for research funding. In addition, NIMH staff have just completed editing a book that describes all active NIMH-funded child/adolescent psychosocial treatment programs. This volume will be widely used in many training programs, and we expect it will help prepare a new cadre of investigators in psychosocial treatments for children and adolescents. Additional NIMH efforts to strengthen the portfolio include a major cross-disciplinary conference on Developmental Plasticity in May of 1996, aimed at facilitating integration of behavioral and neuroscientific approaches to the study of development. Research on developmental plasticity provides the key basic science underpinnings of scientifically based methods for prevention and treatment.

ATTENTION DEFICIT DISORDER AND RITALIN

Mr. Porter: Last year, the committee heard criticism from some outside groups that NIMH was putting too much money into research on attention deficit disorder, and especially into the use of the drug, ritalin. What is your response to this criticism?

Dr. Hyman: As you know, NIMH does not advocate for research on any particular medication per se. Rather, all research, including studies of psychopharmacologic agents, is peer-reviewed for its scientific rigor and public health importance by a panel of independent scientists whose expertise spans all childhood disorders (ranging from autism to depression) and their treatments (from psychotherapeutic to pharmacologic). Because ADHD is the most common childhood behavioral and emotional disorder affecting U.S. children, research on effective treatments is needed. The effectiveness of methylphenidate is already well-established, though it is usually insufficient when used alone. As a result, in the last few years many researchers have sought to identify the optimal treatments for ADHD, including psychosocial treatments used with and without medication. For this reason, we support very few studies focused *solely* on methylphenidate or any other stimulant alone; most of our research involving this medication is looking simultaneously at other therapies that can be used adjunctively. In fact, most of our medication efficacy studies are concerned with establishing the efficacy of treatments for depression, anxiety disorders, bipolar disorder, Tourette's syndrome, and autism.

DR. HYMAN'S INTRAMURAL LAB

Mr. Porter: What is the FY97 budget and FTE allowance for Dr. Hyman's intramural lab? How many of these FTE followed Dr. Hyman to NIH from his former institution?

Dr. Hyman: My intramural lab will be located organizationally in the National Institute of Neurological Disorders and Stroke and will be titled Section on Molecular Plasticity. The Section's operating budget in FY 97 will be approximately \$580,000. This will cover laboratory supplies and salaries for about 3 FTEs and 5 other (Non-FTE) positions such as Visiting Fellows or Intramural Research Training Award Fellows. NIH personnel appointment procedures will be followed in securing adequate staffing for the lab. At this time, I anticipate that 5 research staff with whom I have been collaborating at Harvard have an interest in joining my federal lab in Bethesda.

FY 1995 - 1997 FUNDING AMOUNTS

Mr. Porter: Identify FY 95-97 spending on the following: schizophrenia, depression, bipolar disorder, panic disorder, youth suicide, Alzheimer's disease, eating disorders, and violence.

Dr. Hyman: NIMH funding for the specified disorders for FY 1995 to FY 1997 follows:

(\$ in Thousands)	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
schizophrenia	\$108,900	\$115,236	\$117,387
depression	128,730	136,275	138,954
bipolar disorder	30,772	32,544	33,107
panic disorder	15,532	16,444	16,771
youth suicide	11,755	12,443	12,655
Alzheimer's disease	24,308	25,701	26,128
eating disorders	10,984	11,620	11,831
violence	28,093	29,756	30,381

HUMAN BRAIN PROJECT

Mr. Porter: I assume all of your institutes are involved in the Human Brain Project. Could you describe the objectives of this interdisciplinary project, and which Federal agencies beside NIH are involved?

Dr. Hyman: The Human Brain Project is currently sponsored by 16 Federal organizations, two of which joined in the last year. All of the Institutes that took part in the Brain and Brain Disorders Panel in the Appropriations hearings are participants. NIMH is the lead organization and coordinator for all Federal agencies, NIH institutes, and the university and Federal laboratory supercomputer and information science communities participating in the Human Brain Project. In addition to NIMH, the NIH members include: the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Dental Research (NIDR), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Library of Medicine (NLM), and the Fogerty International Center (FIC). The other participating federal agencies are: the National Aeronautics and Space Administration (NASA), the Department of Energy (DOE), the Office of Naval Research in the Department of Defense (ONR/DOD), and the National Science Foundation (NSF). Representatives from all of these organizations comprise the Federal Interagency Coordinating Committee on the Human Brain Project (FICC-HBP), which coordinates, funds and steers this effort. The coordinating committee precludes unnecessary duplication of effort across Federal organizations and has significantly enhanced the value of the research supported under this initiative. International interest in the project has been expressed by numerous organizations, and efforts are under way to coordinate such research globally.

The Senate requested an update on the progress of this effort (Senate Report 104-145), which is presented in the Congressional Appropriations Committee Report: The Human Brain Project: Forging the New Science of Neuroinformatics.

The long term goal of the Human Brain Project is to provide the means to integrate coherently and comprehensively the vast, diverse and complex data generated by brain and behavioral research. This will increase the efficiency of brain and behavioral research and will accelerate progress in understanding the puzzle of brain function in illness and health. The Human Brain Project supports neuroinformatics research, which knits together the edges of two rapidly advancing and broadly defined areas of science: brain/behavioral science, and informatics, drawing from fields such as information science, computer science, applied mathematics, and engineering. Neuroinformatics is a new area of science, and the Human Brain Project is playing the principal role in its development.

Mr. Porter: Provide a table of the number of institutes and other Federal agencies involved in the Human Brain Project and their financial support.

Dr. Hyman: FY 1995 funding for the Human Brain Project was as follows:

<u>NIH Institutes:</u>	<u>FY 1995 actual funding</u>	
NIMH	\$3,166,154	✓
NIA	173,380	
NICHHD	513,764	
NCI	---	
NHLBI	---	
NIDR	---	
NINDS	390,809	
NIDCD	172,786	
NIDA	1,910,099	
NIAAA	---	
NLM	411,190	
FIC	---	
Subtotal, NIH	<u>\$6,738,182</u>	

Other Agencies:

NASA	250,000
DOE	---
ONR/DOD	---
NSF	200,000

Subtotal, Other Agencies	\$450,000
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TOTAL	\$7,188,182
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SUICIDE

Mr. Stokes: Suicide remains the ninth leading cause of death in the United States, claiming over 32,000 lives last year. Presumably, most of these individuals were suffering from depression. What is the relationship between depression and suicide and what research is the institute doing to address this problem? How much is included in the FY 1997 budget for this initiative and how does it compare with FY 1996, and FY 1995?

Dr. Hyman: Suicide imposes a tragic burden on this country. In addition to the over 32,000 lives lost last year to suicide, the financial burden of suicide is over \$10 billion annually. Depression is a major cause of suicide. However, other serious mental illnesses, especially schizophrenia and bipolar disorder (manic-depressive illness), also have high rates of suicide.

- Schizophrenia - 1 in 10 patients dies by suicide
- Bipolar Disorder - Without treatment (in pre-lithium era), 1 in 6 died by suicide

NIMH has mounted a research initiative to provide a scientifically sound knowledge base for the identification of risk factors and the development of intervention and prevention strategies. Further elucidation of the biological and psychosocial determinants of suicide and suicidal behavior is likely to lead to a better understanding of the underlying mechanisms and the development of novel and effective approaches to treatment and prevention, thereby responding responsibly to continued public and Congressional concern about suicide.

The FY 1997 NIMH budget includes an estimate of \$20,714,000 for research on suicide compared to an estimate of \$20,385,000 in FY 1996 and \$19,266,000 in FY 1995.

NIMH research has shown that the best hope for preventing adolescent suicide is through preventing the underlying mental and addictive disorders which drive young people to suicide. An NIMH-supported pilot study has provided preliminary evidence that a school-based intervention, a group cognitive therapy program, can prevent new cases of depression in a high-risk group of adolescents. This is particularly hopeful because previous intervention designs have been able to reduce symptoms for existing depressions, but not to prevent the onset of new cases.

NIMH supports the DEPRESSION Awareness, Recognition, and Treatment (D/ART) program, a national professional and public education program, which seeks to prevent suicide by reducing depression.

NIMH is collaborating with the National Center for Health Statistics (NCHS) of the Centers for Disease Control, in an ongoing survey -- the National Mortality Follow-back Survey -- to establish just how prevalent is the association between depression (depressive symptoms) and suicide in elderly people. NIMH will also gain information

from this survey about various risk factors for suicide across the life span from the analysis of between-gender, across-age, and other death-comparison groups.

NIMH is working with NCHS on an NIH Office of Research on Women's Health grant supplement award to develop a report on suicide in women.

CLINICAL TRIALS

Mr. Stokes: What are some of your most significant clinical trials, and specifically what can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Hyman: NIMH is pleased to report the following information on clinical trials:

1. Fluoxetine in Anorexia Nervosa R01 MH46687-05

PI: L.K. George Hsu, MD, New England Medical Center, Boston, MA

Underdiagnosed and even trivialized until relatively recently, eating disorders are now recognized as serious mental disorders, predominantly in women. Anorexia nervosa, with a 10% mortality rate, is one of the most lethal mental disorders. While inpatient care, refeeding, and other supportive treatment can restore weight to patients with anorexia nervosa, relapse is common. This trial is comparing the antidepressant fluoxetine (Prozac) with placebo in preventing relapse in women with anorexia nervosa following inpatient care and weight restoration. Recognizing the chronic and recurrent nature of this disorder, 52 weeks of treatment are undertaken. Preliminary data analysis of this ongoing study suggests efficacy of the active medication: to date, among subjects who have completed the 52-week trial, 9 of 13 patients on active fluoxetine are responders, compared with 4 of 11 placebo-treated individuals. During the coming, final year of the study, additional subjects will be treated.

2. A Double-Blind Placebo-Controlled Study of Vitamin E Treatment of Tardive Dyskinesia

Authors: James B. Lohr, MD and Michael P. Caligiuri, PhD

Journal of Clinical Psychiatry 57:167-173, April 1996

Supported by R29 MH45142 (Lohr) and R29 MH45959 (Caligiuri)

This recent publication reported the results of an NIMH-funded clinical trial of vitamin E in the treatment of tardive dyskinesia (TD), a disabling adverse effect of long-term antipsychotic medication. Significant improvement in TD was observed in a group of 17 patients randomly assigned to receive vitamin E, compared to 18 individuals receiving placebo. Results were particularly striking in patients who had experienced TD for no more than 5 years (35% decline in TD ratings during vitamin E treatment) compared to those with more longstanding TD, whose ratings improved by only 11% with vitamin E. These findings are encouraging, given the generally treatment-resistant nature of this serious adverse effect, and emphasize the need for

early diagnosis and intervention in cases of TD.

3. 6-site Multimodal Treatment Study of Attention Deficit Hyperactivity Disorder (MTA Study)

Scientifically valid information is urgently needed concerning the relative effectiveness of the available treatments for attention deficit hyperactivity disorder (ADHD). The 6-site Multimodal Treatment Study of Attention Deficit Hyperactivity Disorder (MTA Study) incorporates recent advances in theory, method, and design in order to address major questions of relevance to national health care reform and health care practitioners' "real world" treatment concerns. The MTA study addresses the question of which treatments (e.g., psychosocial treatment, medication, or both) are most effective for which types of children with ADHD (e.g., characteristics such as comorbidity, gender, family background, etc.); on which domains of child functioning (cognitive, academic, behavioral, peer relations, family relations); and for how long (short vs long term). Through systematic efforts to retain a broad sample of children characteristic of many of those who suffer from ADHD, this five-year study, co-funded by the Department of Education, will be of enormous public health benefit for all ADHD children and their families. One of the most exciting parts of the study has been the unique partnership forged between parents, educators, and clinicians in developing and implementing these treatments for children with ADHD.

4. Intramural Therapeutic Drug Trials

The scientists in the NIMH intramural research program are attempting to predict therapeutic responses from basic and clinical studies of the central nervous system. Early, small scale studies of drugs that potentially have uncharacterized mechanisms of action have led to novel uses for drugs originally developed for other purposes. Several years ago, such a rational approach led intramural investigators to propose the use of anticonvulsant drugs in the treatment of lithium-resistant manic-depressive patients. That treatment has become part of established medical practice. In addition, the NIMH intramural program has extended studies of available drugs to under-researched populations such as children and the elderly. Two examples of the significant recent clinical studies and therapeutic trials are the following:

- NIMH intramural research has provided important insights into the origins of obsessive-compulsive disorder (OCD) in children. Investigations of childhood-onset OCD and Tourette's disorder have identified a subset of patients whose symptoms appear to be mediated through antineuronal antibodies. These antibodies arise in response to Group A beta-hemolytic streptococcal (GABHS) infections (strep throats). This unique subgroup of children with OCD or tic disorders appear to be distinguishable from other forms of OCD and movement disorders and is now identified by the acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections). Identification of this subgroup led to the development of acute and prophylactic treatment protocols. Ongoing treatment studies for this include immunomodulatory interventions (i.e., plasmapheresis, intravenous

immunoglobulins) for Sydenham's Chorea and "antineuronal mediated" OCD and tic disorders. Additionally, a double-blind controlled trial of penicillin versus placebo is underway in a group of children with OCD or tic disorders to determine if they have fewer and less severe exacerbations during the penicillin treatment. The preliminary success of immunomodulatory treatments, such as plasma exchange and intravenous immunoglobulin, suggest that the antibodies play an etiologic role. Despite new, effective pharmacotherapies, OCD remains a debilitating mental illness for many.

- In an innovative study using single photon emission computerized tomography (SPECT) techniques, intramural scientists have demonstrated that patients with Alzheimer's Disease (AD) and normal controls have different responses to longterm exposure to anticholinergic drug treatment. Also with elderly treatment-resistant depressives the investigators have shown that high doses of the anti-Parkinsonian drug, selegiline, are safe and effective as an antidepressant. The SPECT findings are consistent with differential neuronal plasticity responses in the AD and elderly control populations. Given the low percentage of AD subjects who respond to cholinergic agents, further investigations are now ongoing to better understand this process and to take advantage of possible innovative therapeutic implications in a field where there is a paucity of therapeutic options. Elderly depressive subjects are often excluded from research studies because of their age, and they are only rarely treated successfully in clinical settings; therefore the 50% improvement rate in the study with high-dose selegiline represents significant clinical progress for this underserved patient group.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Hyman: The FY 1997 NIMH budget includes an estimated \$57,177,000 for clinical trials. This compares with funding levels for FY 1996 of an estimated \$56,265,000, for FY 1995 actual obligations of \$53,208,000, and for FY 1994 actual obligations of \$52,837,000 for clinical trials.

Mr. Stokes: What is the Institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Hyman: NIMH has always demonstrated its commitment to including women and men and racial and ethnic minority groups and subpopulations in all of its research. All investigators who submit applications for research grants and cooperative agreements and proposals for contracts must follow the NIH policy of including women and racial and ethnic minorities in the study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study. If all populations are not included or are inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be

provided. The extramural and intramural communities have been educated on the requirements of the policy. Grant application forms require applicants to detail the composition of their study populations, and to report on actual accrual when they submit progress reports and apply for renewal. Similar requirements apply to intramural research and contracts.

All NIH-supported biomedical and behavioral research involving human subjects must ensure that women and minorities and their subpopulations are included in Phase III clinical trials, such that valid analyses of differences in intervention effect can be accomplished; not allow cost as an acceptable reason for excluding these groups; and, initiate programs and support for outreach efforts to recruit these groups into clinical studies.

In FY 1995, NIMH took part in a NIH-wide, major initiative to track the enrollment of women and minority persons over the course of funded grants. This initiative will allow the Institute to evaluate the success of the inclusion policy in achieving the goals.

SCHIZOPHRENIA

Mr. Stokes: Are you able to report any progress in the diagnosis and treatment of schizophrenia? I am particularly interested in the development of new medications and the improvement of existing medications which have less side effects than the medications currently on the market.

Dr. Hyman: Schizophrenia, the most chronic and disabling of the severe mental disorders, shatters young lives; and creates enormous burdens for patients, families, and society. More than two million Americans suffer from schizophrenia each year, filling 100,000 hospital beds on any given day. The total annual costs of schizophrenia are estimated at \$32.5 billion. The disorder causes such agony that one of every 10 patients commits suicide. Even with available treatments, most people with schizophrenia continue to suffer chronically or episodically for most of their lives. Multiple lines of NIMH-supported research are now offering hope for understanding the causes of, and developing ways of preventing, schizophrenia.

Newly available treatments, such as clozapine (Clozaril), have helped many people with schizophrenia. Clozapine appears not to have a serious side effect -- the movement disorder, tardive dyskinesia -- caused by other long-term drug treatments for schizophrenia. However, clozapine treatment does carry a risk for a serious blood disorder. For this reason, use of this drug was originally limited to patients who were not helped by other drugs. NIMH research indicates that this treatment may be able to help a much wider group of patients, including young people first experiencing the disease. This is important because the disease worsens with repeated episodes, and this drug helps to protect against the occurrence of such episodes. Clozapine maintenance treatment for schizophrenia saves an average of \$23,000 per patient annually, primarily by reducing the need for hospitalizations. There are also other drugs in the pipeline,

e.g., olanzapine, that promise to be as effective as clozapine without the side-effect blood disorders. Another drug, risperidone, promises to improve treatment for patients who cannot take clozapine.

Evidence continues to accumulate indicating that schizophrenia is a disorder of brain development, caused by a combination of environmental and genetic factors. Insults to the fetus, especially during the second trimester, such as maternal influenza, malnutrition, and RH incompatibility, are all significantly associated with an increased risk for developing this disease. Neuroimaging and other neuro-morphological studies continue to define structural abnormalities in highly defined areas of the schizophrenic brain, particularly the cortex, striatum, and thalamus. Susceptibility to these abnormalities appears to be due to the influence of genes located on as many as five different chromosomes, according to the latest genetic linkage studies. These studies offer great hope for the essential development of new treatments and even preventive strategies.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: For the diseases and disorders that are under the purview of your Institute, where do we stand today with respect to closing the gap in minority health, specifically what progress do you have to report to the subcommittee this year? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Hyman: Epidemiologic data show that there are no racial differences in the prevalence of most mental disorders. However, recent empirical studies, many of which have been carried out in NIMH-supported Minority Research Centers, are confirming cultural differences in the expression of symptoms, resulting in misdiagnoses and inappropriate treatment. The results of these studies are the scientific underpinning for the NIMH's recent contributions to the American Psychiatric Association's Diagnostic and Statistical Manual, DSM-IV. NIMH also is sponsoring studies of ethnically-defined populations as they respond to psychoactive drugs. The results of these studies are beginning to emerge in the scientific literature and have begun to improve the treatment of racial and ethnic minority patients.

MINORITY RESEARCH AND TRAINING

Mr. Stokes: This Institute funds several programs designed to increase research career opportunities for minority students and to improve the research excellence of minority institutions. Specifically, what activities are underway in these areas. Also, what is your projected FY 1997 budget for these activities, and how does it compare with the FY 1996 and FY 1995 funding levels?

Dr. Hyman: NIMH is committed to increasing research career opportunities for minority students and to improving the capability of minority institutions for research excellence. Specific programs include:

- Minority Supplements - NIMH provides funds for administrative supplements designed to provide a continuum of support for underrepresented minority students and scientists. The aim of these supplements is to attract and encourage minority individuals to pursue biomedical and behavioral research careers. The minority supplement program provides scientific opportunities to high school, undergraduate and graduate students as well as individuals in postdoctoral training and minority principal investigators.
- COR - The NIMH Career Opportunities for Research Education (COR) program, formerly the Minority Access to Research Careers (MARC): Honors Undergraduate Research Training Grants, provides support during the junior and senior years of college. Grants are made to institutions with substantial minority enrollments to provide high-level research experiences for promising college students working closely with a faculty sponsor. A Minority High School Science Education Program was added in 1991. This program consists of supplemental awards to active COR grants encouraging minority high school students to select career disciplines related to research on mental and addictive disorders by providing them with hands-on experience working on research projects with faculty and COR trainees over a two year period.
- Minority Fellowship Program - The purpose of the Minority Fellowship Program (MFP) is to ensure that minority investigators assume a prominent position in minority population research. Awards are made to national professional associations in key disciplines: psychiatry, psychology, neuroscience, sociology, nursing and social work. The associations are then responsible for promoting research careers among minority students, screening and selecting trainees, and awarding fellowships for advanced training. NIMH also funded 2 F30 awards, Individual Predoctoral NRSA Fellowships for Minority Students. This is an NIGMS program under which NIMH funds awards with a focus on behavioral science research.
- Dissertation Awards - Dissertation awards are available to minority applicants with approved dissertation proposals enrolled in accredited doctoral degree programs. Up to 25 grants a year may be awarded at no more than \$25,000 in direct costs each. No tuition may be paid under these awards. Small grant support may not be requested for thesis or dissertation research, unless application has been made under the minority dissertation grant announcement - PA 94-053.
- MIRDP/MRISP - The Minority Institutions Research Development Program (MIRDP), was designed to increase the capacity of predominantly minority institutions and enhance the capability of their faculty to conduct rigorous research on mental and addictive disorders. In FY 1995, the announcement soliciting these R24 awards changed the program name to MRISP, paralleling the Research Infrastructure Support Program (RISP). This program is intended to strengthen the research environment of minority institutions by helping these

institutions to augment and strengthen their research infrastructure to facilitate and foster the development of research activities. In FY 1995, NIMH supported eight MRISP awards; four of these are in historically Black colleges and universities.

- NIMH funds 5 research centers that focus on all aspects of mental health related to minority groups:

FY 1995 funding levels

"African American Mental Health Research Center" - R01 MH47182-08 \$805,790

JACKSON, James Ph.D. Research Center for Group Dynamics, University of Michigan, Ann Arbor

These studies will contribute needed information on African American mental health by examining in detail the functions of social support, and the relationships between mental disorders such as depression and the seeking of both informal and professional help.

"Hispanic Research Center" - R01 MH30569-18 \$638,696

RODRIGUEZ, Orlando Ph.D. Fordham University, New York

This center's work focuses on epidemiologic-clinical studies in Hispanic mental health. There are five priority areas of research: emergence of problems, use of services, assessment, effective therapies and rehabilitation. Another goal is to increase the small pool of scholars trained in Hispanic mental health research.

"Nat'l Research Ctr on Asian American Mental Health"- R01 MH44331-08 \$678,684

SUE, Stanley Ph.D. UCLA, California

A landmark community epidemiologic study of mental disorders among Chinese Americans is estimating the prevalence of selected mental disorders and attempting to identify the factors associated with mental health problems in this population.

"National Center for American Indian and Alaska Native Mental Health Research" - (NCAIANMHR) - R01 MH42473-10 \$1,252,423

MANSON, Spero Ph.D. Univ. of Colorado Health Sciences Center, Denver, CO

Fewer than 70 doctoral-level investigators around the country are actively engaged in mental health research among American Indians and Alaskan Natives. Half of the NCAIANMHR's faculty and staff are American Indian, the largest single, programmatic concentration of such professionals in the nation. The Center offers a variety of research and clinical training opportunities. The NCAIANMHR maintains an extensive computerized bibliography on Indian and Native mental health and publishes a refereed journal.

"Research Center on the Psychobiology of Ethnicity" - R01 MH47193-06 \$964,816

LIN, Keh-Ming M.D. Los Angeles County Harbor, UCLA, California

Researchers are examining variations in response to psychoactive medications among minority patients. Several genetically influenced biological systems and environmental differences, could be implicated in the differential effects of these drugs. Other lines of research include assessing the influence of biological, psychosocial and cultural factors in psychiatric morbidity, nosology, and treatment response.

Funding for all of the above activities in FY 1995 - FY 1997 is as follows:

(Dollars in Thousands)	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
Minority Supplements	4,588	4,871	5,037
COR	1,535	1,580	1,580
Minority Fellowship Program	2,602	2,677	2,677
MRISP	3,171	3,263	3,263
Dissertation Awards	415	440	450
Minority Research Centers	4,340	4,606	4,763

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your Institute?

Dr. Hyman: NIMH is pledged to increasing the participation of Historically Black Colleges and Universities (HBCU) in biomedical and behavioral research. The Institute supports a range of research and training opportunities. NIMH also has been strengthening its ties to the HBCUs to encourage mental health and behavioral research. A special effort is being directed to HBCU schools of medicine Departments of Psychiatry as a base for strengthening the infrastructure of these departments. This process should increase these schools' ability to successfully compete for NIMH support. In FY 1995, NIMH supported its first R01 to Hampton University, a school that historically has not been successful with this mechanism in the mental health field. In addition, the NIMH Associate Director for Special Populations sponsors an annual Colloquium for COR students. This meeting enables these highly motivated undergraduate students to come together and present their research to NIMH senior staff, NRSA recruiters, and other mental health professionals. This successful conference has resulted in many of these students being recruited and accepted to the

leading graduate schools in the country.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum. What are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Hyman: NIMH conducts numerous and varied public education activities to promote awareness that mental illnesses are real, common and treatable, to increase awareness that research is the key to advancing our understanding of mental illnesses and brain disorders, and to reduce the stigma of mental illness for patients and their loved ones. The targets of these outreach efforts include several audiences: the general public, mental health professionals, medical professionals, business leaders, advocacy groups and other stakeholders, and the media, through whom many of these publics acquire much of their information on health. All education activities conducted by NIMH are science-based and guided by sound, tested communications principles and strategies.

The major education programs conducted by NIMH are focused especially on depression, anxiety disorders (including panic disorder), and co-occurring disorders. These efforts reach their audiences through multiple channels. In addition, NIMH has targeted minority audiences with specific materials on a wide range of mental disorders. NIMH has made a deliberate effort to depict and represent minorities in publications and has devoted a special section to minority and other special populations in its community outreach kit, which has been distributed to more than 1,000 mental health leaders across the United States. Examples of community outreach include the following:

- NIMH developed and distributed a card, listing NIMH publications targeting women who may suffer from or who may be caretakers of loved ones with a mental disorder. Copies of the card were placed in more than 7,000 supermarkets across the country, primarily in inner-city neighborhoods, and resulted in more than 25,000 requests for publications.
- NIMH produced a series of radio programs on panic disorder, featuring Black mental health professionals and patients, which was distributed through "HealthBeat," an unwired network of Black radio stations.
- At the national Black Family Reunion, held on the Mall in Washington in September 1995, NIMH attracted more than 5,000 people to its pavilion, featuring rap sessions with a Black psychologist, the Harlem Globetrotters, and presentations on depression and attention-deficit hyperactivity disorder.

- NIMH has sponsored seminars and exhibits on panic disorder and other anxiety disorders to educate primary care providers, mental health professionals and the public at meetings of the National Medical Association, the National Black Nurses Association, the South Bronx (N.Y.) Mental Health Council, and other meetings, and exhibited at the Unity '94 conference for minority journalists.
- NIMH and the National Audiovisual Center have distributed 1,700 copies of the NIMH videotape, "Panic Disorder: Stories of Hope," which portrays three patients, one of whom is a Black woman, who have successfully overcome panic disorder; the video also includes an interview with a Black psychiatrist.
- Efforts to reach out to Hispanic Americans have included production and distribution of numerous Spanish-language materials, a number of which are widely advertised through the Consumer Information Center and other organizations. NIMH has produced and distributed Spanish-language public service announcements for television, radio and print media, a videotape, an audio news release, patient screener, and a brochure on anxiety disorders, and is currently producing a photonovela on panic disorder. NIMH has arranged for numerous media placements featuring Spanish-speaking experts on anxiety disorders. Spanish-speaking operators are available at all times to respond to callers to NIMH's 1-800-64-PANIC information line.

The FY 1997 NIMH budget includes an estimate of \$2,593,000 for public education activities compared to an estimate of \$2,637,000 in FY 1996. In FY 1995, \$3,062,000 was spent on these activities, while in FY 1994, NIMH obligated \$2,618,000 for public education and outreach.

Mr. Stokes: In most of the Institutes, these programs are funded in research management and support account, is this the case in your Institute? If so, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are you hurting the most?

Dr. Hyman: The NIMH uses a mix of both its Research Program and Research Management and Support (RMS) accounts to support ongoing public education and outreach efforts. Recent reductions in available RMS funds have required the Institute to make a number of hard choices in terms of what it can support. This includes the following:

- NIMH has passed up several public outreach opportunities. For example, the Consumer Information Center (CIC) organizes promotions to provide health education materials to select audiences, such as Railroad Retirees, Veterans' benefit check recipients, and Office of Personnel Management retirees. In the current fiscal year, NIMH has turned down opportunities to participate because of lack of funds for handling and mailing costs, and for printing sufficient materials.

- For similar reasons, and because participation would have further overburdened staff responsible for responding to inquiries and providing fulfillment services, NIMH has had to forego opportunities from the media, organization newsletters, etc., to be listed as a resource for mental health information. These opportunities have had to be passed on to advocacy groups and to the Center for Mental Health Services.
- In years past the Institute managed an exhibit program to provide professional education outreach at the annual meetings of many professional associations and to the public at health fairs and other public events. Due to the loss of FTE's, a severely reduced travel budget, and no monies for exhibit design and construction, NIMH has had to phase out the Institute exhibit program.
- NIMH has had to make the hard decision to eliminate small professional services contracts, which allowed us to arrange for special education and outreach programs at various events and meetings and to travel to such events and make presentations on the Institute's outreach programs.

It should be noted that NIMH is currently undertaking an indepth review of its science education program activities to ensure maximum impact for monies spent.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between your institute and the office of research on minority health? Are there specific projects in your institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Hyman: There are currently no collaborations underway between NIMH and the Office of Research on Minority Health (ORMH), but discussions are underway for greater interactions with ORMH in FY 1996. No NIMH projects were totally funded by the ORMH in FY 1995.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Hyman: Each year the NIH ORMH solicits recommendations for projects to cofund. In FY 1995, ORMH had as one of its priorities to strengthen and expand its support of minority research supplements, with the aim of increasing both the number of minorities entering careers in biomedical research and the number of minority researchers who successfully apply for NIH investigator - initiated research grants. During FY 1995 ORMH co-funded one NIMH project, Cholinergics and Sensory Gating in Schizophrenia (R01MH50787).

ORMH support for this project was \$75,550 for one year which constituted 36% of the total funding. NIMH supported the remaining 64%, \$131,798, for a total award of \$207,348.

GENE THERAPY

Mr. Stokes: How critical is gene therapy research to furthering advances in areas of research which are under the purview of your Institute? What diseases and disorders would benefit from enhanced research in this area?

Dr. Hyman: Gene therapy research holds considerable promise for correcting the genetic errors that cause certain inherited diseases, once those genetic errors have been identified. At present, research on the genetic bases of mental illnesses is concentrated on identifying the genes, and the products of the genes, that contribute to mental illnesses. We have some very good news about the progress of this research. Within the last year or two, researchers have pinpointed the regions of the genome (DNA) in which the genes for both schizophrenia and manic-depressive illness (bipolar disorder)—both severe mental disorders affecting large numbers of people—appear to be located. Scientists, working together with patient/family populations, will then be able to identify exactly which genes are involved, what the genes do normally, and how defects in the genes lead to these illnesses. At this point, research on gene therapy to correct these genetic mistakes could become of enormous importance for the treatment of mental illnesses, although the difficulties of such an approach in what are likely multi-gene disorders will be formidable.

NIMH intramural researchers, in collaboration with other NIH intramural scientists, are developing gene-therapy treatment approaches for the rare hereditary disorder, Gaucher disease, for which the abnormal gene is known. In this disease, an inherited deficiency of the enzyme beta-glucocerebrosidase leaves the body unable to break down and dispose of complex fatty substances in the bloodstream, resulting in their accumulation in the spleen, liver, and bone marrow, and causing severe neurologic and other effects, including early death. These researchers have developed a recombinant form of glucocerebrosidase used in enzyme therapy.

Currently, we are supporting a significant number of basic and clinical researchers who are studying viral vectors, antisense nucleotides, and transgenic animal models, all of which are extremely valuable in laying the groundwork for successful application of the gene therapy approach.

NATIONAL INSTITUTE ON DRUG ABUSE

FEDERAL DRUG INVESTMENT

Mr. Porter: Dr. Leshner, could you begin by giving us an overview of the Federal drug investment? How much do we spend on research versus treatment versus prevention versus interdiction?

Dr. Leshner: The Federal drug investment supports a comprehensive program of demand and supply reduction activities which are directed to the overall goal of reducing illicit drug use and its consequences. These activities support the five goals of the 1996 National Drug Control Strategy which are to: motivate America's youth to reject illegal drugs and substance abuse, increase the safety of America's citizens by substantially reducing drug-related crime and violence, reduce health, welfare, and crime costs resulting from illegal drug use, shield America's air, land, and sea frontiers from the drug threat, and break foreign and domestic drug sources of supply.

	<u>FY 1995</u>	<u>FY 1996</u>	<u>FY 1997</u>	<u>Change</u>
	(dollars in millions)			
NIDA's budget*	\$436.9	\$458.4	\$466.3	+1.7%
Total Federal Drug Control Spending	13,251.2	13,783.5	15,063.5	+9.3%
Drug Prevention	1,559.1	1,430.1	1,591.6	+11.3%
Drug Treatment	2,692.0	2,679.4	2,908.7	+8.6%
Interdiction	1,280.1	1,339.4	1,437.2	+7.3%

* 1) NIDA's budget = 3.3% of total Federal drug control spending in FY 1995, FY 1996.

2) NIDA's budget is part of the Drug Prevention and Drug Treatment totals.

Mr. Porter: Do you think that the balance of funding between the demand and supply sides is appropriate?

Dr. Leshner: The President's drug strategy is a balanced, comprehensive approach to reducing illicit drug use and its consequences. This approach recognizes that a broad range of activities, including treatment, prevention, education, research, criminal justice, and interdiction efforts are needed to address the health and social problem which drug addiction brings in its wake.

TRENDS IN DRUG USE

Mr. Porter: What do the latest surveys show about trends in drug use? Are there increases in use among all age groups and all types of drugs or are the trends mixed?

Dr. Leshner: Based on the latest findings from the National Household Survey on Drug Abuse (NHSDA), conducted by the Substance Abuse and Mental Health Services

Administration (SAMHSA), the rate of current illicit drug use, i.e., use within the past 30 days, among persons 12 years of age and over did not change from 1993 to 1994. Considered by age group, current use rates did not change for young adults 18-25, persons 26-34, or those 35 and older. However, current illicit drug use increased significantly for youth aged 12-17 between 1993 and 1994.

More recent data from the 1995 Monitoring the Future Study (MTF) show that drug use among youth has continued to rise. Between 1994 and 1995 use of cigarettes and most illicit drugs increased among students in all three grades surveyed in the MTF. In addition, fewer students expressed negative perceptions of drug use. In most cases, these changes continued recent trends that began in the early 1990s and reversed a decade or more of decreases in drug use.

COCAINE ADDICTION PHARMACOTHERAPY

Mr. Porter: You have recently issued an RFA for 'Strategic Programs for Innovative Research on Cocaine Addiction Pharmacotherapy' to expedite the clinical application of anticocaine medications. What will this new effort provide that is not available from the other medications development centers and contracts you presently support?

Dr. Leshner: One of the objectives in the development of medications for cocaine dependence is to involve a plurality of approaches with multiple groups. Medications development centers permit the clinical testing of candidate potential medications formulated by academic researchers. Contracts support directed preclinical and clinical studies. In addition, we believe there is a need to further involve academic and pharmaceutical industry researchers. This will create new and potentially novel scientific, strategic, and commercial partnerships between academic, government, and industry. Further, while most of NIDA's medications development efforts are currently centered on aspects of modulation of the dopamine system, this RFA is designed to stimulate applications in other areas and generate new ideas and alternatives.

The RFA also attempts to fill a gap between the generation of preclinical findings and the testing of a concept in a clinical study. In this manner, it will bring together bench scientists and clinical groups attempting to move from the lab to the clinic in potentially unique collaborations. Moreover, collaborations are not limited to academic groups. It is entirely possible that a commercial (biotechnology or pharmaceutical) group will develop a partnership with an academic group.

RESEARCH CENTERS

Mr. Porter: You have recently conducted a review of your research centers program. Tell us what changes you intend to make in the criteria for the types of centers you support, and whether you expect the share of your budget designated for centers to change over time.

Dr. Leshner: Shortly after becoming the NIDA Director, I determined the need for a

comprehensive review and assessment of NIDA's center grant program. This review included soliciting views from the field, site visits to selected center grantees, and extensive discussions with NIDA's Extramural Science Advisory Board and the National Advisory Council on Drug Abuse. Based on the information we gathered, NIDA developed its Research Center Grant Guidelines which were issued in September 1995 (and revised with minor changes in December 1995).

Receiving a NIDA center grant is a tremendous honor; it recognizes superior scientific leadership, research productivity and quality, and the ability to bring together a team of scientists who can conduct innovative cutting edge research. Regarding criteria for center grant support, NIDA will only support center grants that: demonstrate the concept of "centeredness," that is, identification of the essential relationship of each component part to the overall theme of the center and demonstration that the "whole of the center is greater than the sum of its parts." Centers must apply multiple scientific perspectives and approaches to address the problems of drug abuse and addiction and foster inter- and multi-disciplinary collaboration and coordination. Thematic integration is another defining feature of center grants. They are intended to serve as an enabling mechanism for the conduct of innovative, state-of-the-art research on drug abuse and addiction that could not or would not be conducted without the center. In addition, centers must serve or demonstrate the potential to serve as regional or national research resources. NIDA center grantees are expected to attract both established and promising investigators into drug abuse research and provide opportunities for research training, career development, and mentoring.

The share of NIDA's budget to be spent on center grants will depend on research opportunities as well as the quality of applications received. The policy change was not based on budgetary outcome.

REINVENTION CHANGES

Mr. Porter: Your budget justification indicates that you have made significant changes in your Institute as part of the "reinvention" process, both administratively and programmatically. Highlight a few of these changes for us and tell us what impact you expect them to have on administrative costs and program efficiency?

Dr. Leshner: Over the past year, NIDA has undertaken a number of activities to increase the efficient utilization of its resources and ensure their availability to support the research mission of the Institute. Innovations in administration and program management include NIDA's participation in NIH Competitive Service Centers, informal resource sharing, a recent reorganization of administrative services, and significant decreases in the use of the contract versus grant mechanism for research program support.

The Service Center program was developed and established by NIH to enable institutes to receive and provide services to each other, building upon the principles of economies of scale and focused expertise to improve efficiencies while ensuring quality services. To highlight one service center example, NIDA's Intramural Research Program (IRP) receives services from the National Cancer

Institute (NCI) in Technology Transfer. The service center provides assistance in the negotiation of technology transfer agreements such as Cooperative Research and Development Agreements (CRADAs), and Material Transfer Agreements (MTAs), and other collaborative agreements to advance the commercialization of institute technologies. Use of the service center has been a success in two ways. The institute has been able to redirect resources to research programs, with NIDA staff no longer responsible for certain technology transfer activities. In addition, royalty income is expected to increase as a result of a greater number of cooperative research agreements.

Opportunities for resource sharing exist for programs of three NIH Institutes located in Baltimore, NIDA's Addiction Research Center, National Institute on Aging's (NIA) Gerontology Research Center, and a laboratory of the National Center for Human Genome Research. One example is library services, and visual media and graphics services that are shared and save each Institute dollars and FTEs because of their common location. Another example is a new Positron Emission Tomography (PET) facility at NIDA being shared with NIA, which allows fuller utilization of the technology. This arrangement is mutually beneficial with NIDA receiving program income for use of the equipment, and NIA gaining access to a state of the art machine in closer proximity than was previously available.

Some restructuring of administrative services is occurring. For example, the personnel management and management analysis and services branches have been consolidated. This action, which takes advantage of NIH re-engineering activities in the human resource management area, has already achieved professional and support staff reductions and is expected to achieve further FTE reductions over the longer-term. Further, administrative services are also expected to improve because rather than having individuals specializing in an administrative function, staff now work in teams of generalists that can provide backup for one another when there are absences.

As part of a review of management of research programs, NIDA conducted an assessment of the use of particular mechanisms for funding grant and contract programs. One result has been a decrease in the use of the research and development contracts mechanism. It was determined that projects previously supported through the contracts mechanism could more effectively and appropriately be supported and performed as research grants. Reducing the funding through the contracts mechanism has also meant enhanced availability of funds for the competitive grant mechanisms. Since FY 1994, NIDA has increased funds for research project grants by 16% and has reduced funding for contracts by over 13%.

HUMAN BRAIN PROJECT

Mr. Porter: I assume all of your Institutes are involved in the Human Brain Project. Could you describe the objectives of this interdisciplinary project, and which Federal agencies beside NIH are involved?

Dr. Leshner: The Human Brain Project is currently sponsored by 16 Federal organizations, two of which joined in the last year. All of the Institutes that took part in the Brain and Brain Disorders Panel in the Appropriation hearings are participants. The National Institute of Mental Health (NIMH) is the lead organization and coordinator for all Federal agencies, NIH Institutes, and the university and Federal laboratory supercomputer and information science communities.

participating in the Human Brain Project. NIDA has been involved from the very inception of the project and is also a major supporter. In fact, in FY 1995 NIDA's investment in the project was one of the largest. Other participating NIH members include: the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Dental Research (NIDR), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Library of Medicine (NLM), and the Fogerty International Center (FIC). The other participating federal agencies are: the National Aeronautics and Space Administration (NASA), the Department of Energy (DOE), the Office of Naval Research in the Department of Defense (ONR/DOD), and the National Science Foundation (NSF). Representatives from all of these organizations comprise the Federal Interagency Coordinating Committee on the Human Brain Project (FICC-HBP), which coordinates, funds, and steers this effort. The coordinating committee precludes unnecessary duplication of effort across Federal organizations and has significantly enhanced the value of the research supported under this initiative. International interest in the project has been expressed by numerous organizations, and efforts are under way to coordinate such research globally.

The participants are pleased that the House is interested in this important, cross-cutting activity. The Senate requested an update on the progress of this effort (Senate Report 104-145), which is presented in the Congressional Appropriations Committee Report: The Human Brain Project: Forging the New Science of Neuroinformatics.

The long-term goal of the Human Brain Project is to provide the means to integrate coherently and comprehensively the vast, diverse and complex data generated by brain and behavioral research. This will increase the efficiency of brain and behavioral research and will accelerate progress in understanding the puzzle of brain function in illness and health. The Human Brain Project supports neuroinformatics research, which knits together the edges of two rapidly advancing and broadly defined areas of science; brain/behavioral science, and informatics, drawing from fields such as information science, computer science, applied mathematics, and engineering. Neuroinformatics is a new area of science, and the Human Brain Project is playing the principal role in its development.

Mr. Porter: Provide a table of the number of institutes and other Federal agencies involved in the Human Brain Project and their financial support.

Dr. Leshner: FY 1995 funding for the Human Brain Project was as follows:

<u>NIH Institutes</u>	<u>FY 1995 Actual Funding</u>
NIMH	\$3,166,154
NIA	173,380
NICHD	513,764
NCI	---
NHLBI	---
NIDR	---
NINDS	390,809

NIDCD	172,786
NIDA	1,910,999
NIAAA	---
NLM	411,190
FIC	---

Other Agencies

NASA	250,000
DOE	---
ONR/DOD	---
NSF	200,000

EXTENT OF DRUG PROBLEM

Mr. Stokes: Can you give me an update of the extent of drug use in this country, and where do we rank internationally? Are there specific age groups in which we are seeing a decline, or in which we are seeing an increase?

Dr. Leshner: Data from the 1994 National Household Survey on Drug Abuse (NHSDA) show that 34.4 percent of the United States population 12 years of age and over have used an illicit drug at least once in their lifetime; 10.8 percent reported illicit drug use in the past year, and 6.0 percent had used in the past month.

Focusing on use of specific types of drugs in the past year, the 8.5 percent of the population 12 and over reported using marijuana; 1.7 percent reported using cocaine (including 0.6 percent using crack); 1.3 percent used hallucinogens; and 1.1 percent used inhalants. Past year nonmedical use of psychotherapeutic drugs was reported by 2.9 percent of the 12-and-over population, including 0.7 percent using stimulants, 0.4 percent using sedatives; 1.1 percent using tranquilizers, and 2.0 percent using analgesics.

As suggested in this question, trends in drug use differ by age group. Data from school students collected in the Monitoring the Future (MTF) study have shown increases in the use of several categories of drugs from 1991 or 1992 through 1995. Prominent among these increases has been a growth in the use of marijuana.

Consistent with observations in the school-based MTF study, the household-based NHSDA survey found that illicit drug use rates increased from 1993 to 1994 among persons 12-17 years old. However, the NHSDA found no significant change in the rate of illicit drug use from 1993 to 1994 for each major age group 18 and older.

In the past the United States has been cited as having the most serious substance abuse problem in the industrialized world. This claim, however, is difficult to substantiate because little valid and reliable information on drug use is available for many--if not most--other countries. Sophisticated epidemiologic surveys and monitoring systems have been in operation in the U.S. for decades, so information on drug use in this country is widely available. As comparable data are not available for most other countries, the relative ranking of the U.S. in drug abuse severity is not known. However, the limited data that are available suggest that most countries of the world have substantial drug abuse problems ranging from inhalant use among street children to misuse of medical prescriptions among the elderly. Drug abuse and drug dependence are global and complex.

Mr. Stokes: What is the cost of drug abuse to the nation?

Dr. Leshner: Drug-related economic cost estimates attempt to capture the multidimensional nature of the societal burden that results from drug abuse and addiction. Estimates include direct costs resulting from medical consequences, co-occurring mental health problems, premature deaths, drug-related HIV/AIDS and infectious diseases such as tuberculosis and hepatitis. The

economic burden on society also encompasses the use of costly technology and legal and judicial resources, significant losses in productivity for both victims of crime and incarcerated perpetrators of drug-related crimes, and other indirect costs associated with property destruction, serious accidents, insurance, employment and social welfare.

In 1990, economic costs of drug abuse were estimated to be \$67 billion. It should be noted that this is an updated estimate based on 1985 data, which was revised to reflect inflation and population changes (Dorothy Rice, 1985 and Rice et al., 1980). As a result of important advances in our knowledge about the nature and impact of drug abuse and addiction, the 1990 figure underestimates costs in several areas which have changed dramatically over the eleven years since the original study.

New estimates are currently under development that will incorporate data reflecting the significant increases in drug-related criminal justice expenditures and the growth and expansion of the crack-cocaine and the AIDS epidemics, with IV drug users and their sexual partners comprising the fastest growing segment of the HIV population. In addition, the revised estimates will reflect medical and social costs associated with the resurgence of TB and hepatitis, which has been fueled by drug addicts, as well as costs resulting from prenatal exposure to drugs.

PROGRESS IN EFFECTIVE TREATMENTS

Mr. Stokes: How far away are we from having an effective treatment for any of the major drugs of abuse, like cocaine?

Dr. Leshner: NIDA research has successfully developed several effective treatments for the major drugs of abuse. NIDA has developed LAAM for the treatment of narcotic dependence. It is now approved in 40 states. An opiate partial agonist, buprenorphine, is being developed as a treatment for opiate abuse. We are developing two formulations of this product, a buprenorphine tablet and a combination tablet with an antagonist, naloxone. We expect the pharmaceutical firm we are working with on this project to file NDAs for approval in mid-1997. This will yield three drug products for the treatment of narcotic dependence since the program was formed 7 years ago.

Much progress has been made on the development of behavioral treatments for drug abuse since the inception, in 1993, of NIDA's Behavioral Therapies Development Program. Two behavioral therapies show great promise for the treatment of cocaine abuse. One is cognitive-behavioral therapy, which has been shown not only to effectively reduce cocaine use by the end of treatment, but to remain efficacious for some time after the treatment has ended. Also, a behavioral intervention using vouchers as a reinforcer for abstinence from cocaine has been shown to promote initial abstinence from cocaine. For polydrug abuse in adolescents, a variety of forms of family therapy have been shown to be efficacious. For opiate dependence, a combination of methadone with a number of behavioral interventions, such as supportive-expressive therapy, contingency management, and family therapy, has been shown to be effective.

NIDA's strategy for developing a medication for cocaine dependence relies on both opportunistic and strategic elements. In the former, we are currently performing clinical trials with over 20 different marketed psychotropic agents. Should one of these prove effective in reducing cocaine usage or preventing relapse to cocaine use, a treatment could be found in the short-term (2-3 years). Since this group of drugs is marketed, they could be prescribed before a supplemental filing is made to the FDA. For example, there have been three studies which reported that desipramine, an antidepressant drug, reduced or eliminated cocaine use compared to a placebo treatment. These trials were performed in intranasal users. Desipramine appears to be moderately effective in this group but is less effective or ineffective in crack cocaine users. We believe this is because crack cocaine users develop a more severe form of dependence.

NIDA is systematically evaluating marketed drugs as either agonist replacement or antagonist therapies. We are testing several medications (amphetamine, methylphenidate, phentermine, diethylpropion) that are orally active psychostimulants in agonist replacement studies. These studies will test the feasibility of an agonist medication producing a decrease in cocaine use.

We are also testing antagonist medications. Most of these drugs are powerful anti-psychotic medications and may have powerful side-effects. Work is proceeding cautiously in this area.

We are also testing naltrexone in cocaine dependent subjects who are also dependent on alcohol. Naltrexone, developed by NIDA in the mid-1980s for relapse prevention in opiate addicts, has been shown to be effective in reducing relapse in alcoholics. The intent is to determine if reduction or elimination of alcohol use will reduce cocaine use concomitantly.

There is also evidence to suggest that high doses of methadone, given in treatment settings, in dually dependent subjects (dependent on both opiates and cocaine) reduces both opiate and cocaine use. A clinical trial of buprenorphine in dually-dependent subjects also reported that the high dose buprenorphine group had lower opiate and cocaine use.

Our strategic efforts are aimed at following new leads generated by preclinical and clinical pharmacology studies. We have several new findings we are excited about that may lead to new treatments for cocaine dependence.

Several basic science discoveries have been made that point out new directions for medications development for cocaine abuse. Although these new developments will take years to capitalize on, the scientific basis for developing medications for cocaine abuse is stronger than ever. During the past year, investigators have reported that dopamine agonists (D1 subtype but not D2 subtype) reduce cocaine self-administration in relapse models. This suggests that parts of the dopamine system may be involved in relapse to cocaine abuse, giving us a target for medications development. Moreover, some very slow onset dopamine transporter (one of the sites that binds cocaine in the brain) drugs have been synthesized. These drugs have durations of action measured in days, suggesting the potential for dosing twice a week or less of an agonist replacement medication.

Dopamine autoreceptor agonists have been shown to block self-administration of

amphetamine and cocaine without themselves being self-administered. The properties of these potential drugs are unique among dopamine agonists and antagonists insofar as drugs in this class possess properties of both types.

Kappa opioid agonists have been shown to block sensitization to cocaine and to block self-administration, giving us another avenue of approach to this disorder.

Another class of drugs which antagonize the glutamate system, so called NMDA antagonists, have shown an effect to reduce cocaine self-administration in rodent models. Clinical testing of two NMDA antagonists will begin this year in an opiate dependent population.

During the last year, biological approaches to reducing cocaine abuse have taken a giant step forward. Two groups have produced "cocaine vaccines" in rodent species. NIDA plans to test this concept as soon as a clinical investigational vaccine is available. This could possibly occur as early as January, 1997. Moreover, we have been negotiating with a pharmaceutical firm to test an enzyme which metabolizes cocaine into non-psychoactive substances. This could be useful in treatment of cocaine toxicity in emergency room settings as well as be used as a chronic medication. We have also identified several compounds that appear to stimulate levels of this enzyme in the bloodstream, suggesting another route whereby the enzyme system could be fortified to increase cocaine metabolism. It is anticipated this would result in a lesser effect of cocaine per each administration, facilitating extinction of the drug-taking behavior.

Of course, just as no one medication is always effective for every person, no behavioral intervention has been shown to be completely efficacious for every drug abuser. Researchers continue to examine the question of which therapies are best therapies for which individuals. For example, it appears that opiate addicts with psychiatric problems do better with cognitive behavioral therapy or supportive-expressive therapy than with drug counseling. More is being learned each year about the particular types of interventions that are best for particular types of individuals.

PREVENTION

Mr. Stokes: What progress have we made in prevention research to solve the problem of drug abuse and addiction?

Dr. Leshner: Over the past ten years, NIDA prevention research has developed significant scientific evidence that supports the efficacy and effectiveness of a number of theory-based drug abuse prevention interventions that have been tested under rigorous controlled conditions. For example, prevention research indicates that adolescent drug abuse can be prevented with implementation of comprehensive drug preventive interventions and delivered through a combination of strategies to include drug education in the schools, parent education, health policy, anti-drug abuse media campaigns, and community organizations to combat drug abuse at the local level.

Drawing from randomized controlled group research, the science of prevention suggests that

effective drug abuse prevention programs: 1) build social competency, 2) strengthen drug resistance skills, 3) increase factual knowledge of the negative social and medical consequences resulting from drug consumption, 4) reinforce anti-drug use norms at the individual, school, and community level, 5) are developmentally appropriate, 6) address the unique needs of minority sub-populations, and 7) provide relevant prevention training along the life span (elementary, middle school, high school, the workplace, college, etc.) with adequate booster sessions to reinforce the prevention message.

More recently, NIDA has been encouraging the prevention field at the State and local level to implement drug abuse policy and programs that are built upon scientific knowledge as developed through research sponsored by NIDA and sister agencies in the NIH and the Public Health Service. This research suggests that State and local programs should implement programs for a wide range of audiences to include: the general population (Universal Prevention Intervention), sub-populations with identified drug use risk factors (Indicated Prevention Interventions) and individuals and sub-groups that are already experiencing multiple behavioral problems to include experimentation with a variety of psycho-active substances (Selective Preventive Interventions). This approach to comprehensive programming in prevention was recommended by an Institute of Medicine study on prevention research in mental health and addictive disorders that was requested by the U.S. Congress.

The report, edited by Mrazek and Haggerty was published in 1994 and was titled: Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research (National Academy Press).

NIDA sponsored drug abuse prevention intervention research indicates that the most critical components of effective **UNIVERSAL, INDICATED, AND SELECTIVE** drug abuse prevention programs include:

1. Presentation of scientific evidence of the harmful consequences of drug use.
2. Establishment of clear anti-drug use attitudes and norms at the individual, family, peer group, and community level.
3. Drug refusal skills training.
4. Prosocial skills training in problem identification and problem solving, goal setting, interpersonal communication, and anger management.
5. Family management skills training in monitoring adolescent activities, setting family rules, positive discipline practices, reduction in negative parenting actions, problem solving tactics, anger management, and effective interpersonal communication.
6. Development of a community-based prevention coalition which advances a number of prevention strategies to include elimination of open-air drug markets, planning of community sanctioned alternative drug-free activities and events for youth, adoption

of laws, regulations, and policies that support drug-free schools, communities, and places of work.

7. Persuasive and persistent anti-drug media coverage to inform the community about the continued dangers of drug abuse and to prompt local and legislative actions to curtail drug use and drug trafficking in local neighborhoods.

8. Adoption and enforcement of drug abuse prevention focused health policies relevant to prohibitions against drug use in schools, the workplace, and neighborhoods.

DIVERSITY

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your Institute?

Dr. Leshner: We have been working to increase the interest and participation of African American and other minority research investigators in drug abuse related research for a number of years. Within the last year we have continued some efforts and expanded still others. These include the following initiatives with selected activities described.

Historically Black Colleges and Universities Initiative (HBCUs)

Implementation of this initiative began in 1994. Its overall purposes are to strengthen the research infrastructure, provide drug abuse research experiences, and assist in equipment needs of HBCUs. Activities of the last year include the following:

- Research and development technical assistance sessions were held with faculty and administrators from 10 HBCUs (Jackson State, Delaware State, University of Maryland - Eastern Shore, Langston, Kentucky State, University of Arkansas at Pine Bluff, Grambling, Florida A & M, University of Virgin Islands, South Carolina State). Schools are making short- and long-term plans for drug abuse research focusing on resource and faculty development/support needs. Research is being pursued in the areas of treatment and prevention interventions.
- An HBCU supplement program was begun on a trial basis. Nine awards were provided to faculty and students at HBCUs (Howard, Central State, Meharry, Jackson State, Norfolk State, Morehouse, Drew) to allow them to work with current NIDA grantees (at universities such as Loyola, Cornell, Cleveland State and Morris Brown) in a productive and flexible arrangement. Research areas they are pursuing include work on opioids and the physiology of the ventral pallidum, crack distribution, opioid peptide analogs as obstetrical analgesics, effects of drugs on cognitive functioning, neurobehavioral function among cocaine abusers, HIV risk reduction for substance dependent adolescents, and mother's drug treatment and children's resiliency.

- The research center established at Howard University's College of Medicine has been supporting faculty and student development. Collaborative efforts with other HBCUs and community organizations have been initiated. In addition, a number of lectures have been sponsored for medical students and staff and others to encourage interest in drug abuse research.

Underrepresented Minority Supplement Program

This program was expanded with \$1.4 million provided in FY 1995 and \$1.2 provided in FY 1996 for new recipients. About fifty new investigators and students were funded in the last year. In addition, a meeting of selected supplement recipients is scheduled for the summer of 1996 to encourage and assist them in preparing to become independent investigators.

Research Development Seminar Series

NIDA provides research development workshops to women and minorities. Within the last year, sessions were held with approximately 35 minority investigators. Areas of research concentration included Hispanic community research concerns and interests of nurse researchers.

Special Issue Meetings and Workshops

NIDA has met in separate workgroups of Hispanic and African American researchers and scholars to discuss issues of particular concern to those communities. These meetings have been important in identifying approaches that can be taken to increase the participation of minorities in drug abuse research. NIDA is supporting a mini-conference on drug abuse research in Hispanic communities and Hispanic researcher development at the annual meeting of the College of Problems of Drug Dependence (CPDD) in June, 1996.

With support from the Office for Research on Minority Health, selected workgroup members who are current grantees have planned workshops/meetings to prepare researchers to become involved in drug abuse research and to help NIDA better understand barriers to nonparticipation. Four such meetings are planned. They focus on (1) community-based research needs and researchers (two meetings were supported, the first will be held in New Orleans in July, 1996), (2) factors contributing to African-American researcher development, and (3) establishing collaborative relationships (scheduled for October, 1996 in Los Angeles).

Minority Researchers Funded

Some new minority investigators were funded/approved for funding within the last year. At least three had been participants in the seminar series.

MARC

NIDA increased its allocation for the MARC program this year, and is working with the NIH coordinator to plan how to become more active with the NIH program.

NEW INITIATIVES

Mr. Stokes: What new Initiatives have your Institute identified for implementation with respect to African-American women?

Dr. Leshner: The programs described above have a high participation of African American women and men. New program announcements expressed interest in minorities and women, however.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials underway at the Institute, specifically what can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Leshner: We have preliminary results from two studies, involving the anti-epileptic medications dilantin and lamotrigine, that suggest a salutary effect in reducing cocaine abuse. Follow up studies are being conducted.

One of our grantees has determined that low doses of orally administered cocaine can be given without developing safety problems. Moreover, these individuals do not get a high from the oral cocaine although the effect of intravenous cocaine challenges is blunted. Similar work is being conducted in our intramural research facility. The results to date suggest that an orally administered agonist may be useful in modulating responses to cocaine abuse, thereby assisting abusers in stopping cocaine intake.

Cocaine craving studies have been conducted in two sites that use brain imaging techniques to see which areas of the brain are activated during craving. Areas of the limbic system and frontal lobe show increased blood flow and increased metabolism to stimuli associated with cocaine-related stimuli. These findings suggest that this method can be used to study craving and its alleviation. Moreover, we are aware of certain drugs which may reduce activity in the activated brain regions. We can then prospectively test whether these drugs reduce craving and drug use.

Brain imaging studies have determined that a certain area of the frontal lobe, the orbital frontal cortex, appears to be altered in chronic cocaine abusers. Initially, this region exhibits a hypermetabolic state when subjects are using cocaine or early during withdrawal. Later withdrawal shows a decreased metabolism in this brain region. The findings are of interest in that this brain area is associated with repetitive, compulsive behaviors and decision-making. Studies are underway now to test whether decision-making ability is altered in these individuals. If a cognitive defect is found, it would add another piece to the puzzle of the chronicity of drug intake in that such individuals may have a defective decision-making ability. Another type of

imaging, MRI, has shown that chronic substance abusers have a reduction in brain volume in the portion of the frontal lobe that contains the orbital frontal cortex. It is not known whether the antedates drug use or is a consequence of it.

There are currently clinical trials underway on cognitive-behavioral therapy, contingency management, family therapy, cue exposure and aversive conditioning. Results from trials in progress, of course, are not available at this time. Much behavioral therapy research with drug addicts is in the "pre-clinical trial" stage. That is, just as the development of new medications for diseases must take place before the medication is subjected to a clinical trial, the development of behavioral therapies must take place before they are tested. The process of behavioral therapy development is not immediate, and results regarding innovative behavioral therapies for drug addiction, currently under development, will not be available for a number of years.

There are some additional significant findings to report. First, as mentioned above, cognitive behavioral therapy with cocaine addicts appears not only to be effective, but to remain effective well after treatment ends (i.e., one year). This has also been shown with alcoholics receiving naltrexone, adding weight to the finding. Second, the use of vouchers with cocaine abusers has been shown not once, but twice, to promote abstinence from cocaine, suggesting that it may be a valuable approach to pursue. Third, the evidence that family therapy is effective with adolescents continues to accumulate.

Also, a Tuberculosis prevention study among IDUs testing four alternatives for the delivery of chemoprophylaxis with isoniazid (INH) has found that large numbers of out of drug abuse treatment IDUs can be screened for TB infection outside of institutional settings and with the use of monetary incentive (very high return rates (90%) for skin test reading can be achieved at 48 hours post-test).

Mr. Stokes: How much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994.

Dr. Leshner: The funding levels for the National Institute on Drug Abuse for clinical trials are:

<u>FY 1994</u>	<u>FY 1995</u>	<u>FY 1996</u>	<u>FY 1997</u>
\$71,245,000	\$71,948,000	\$73,300,000	\$74,900,000

Mr. Stokes: What is the Institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Leshner: NIDA has been very responsive to this initiative. We have issued a policy statement to our grantees that women and minorities should be included in all relevant clinical trials unless a clear and compelling rationale and justification is provided that inclusion is inappropriate to the health of the subjects or the purpose of the research. This language is included in all NIDA Program Announcements and RFAs.

In trials sponsored by NIDA's intramural research program and the Medications Development Program, similar policies have been communicated and incorporated into the "Standard Operating Procedures" for clinical trial enrollment.

The appropriate representation of women and minority groups in clinical trials is both a consideration at the time of peer review of grant applications and at the time of award. NIDA has established a Women and Gender Research Workgroup with representation from all Institute Divisions and Offices to encourage research and research training and research dissemination related to women and gender.

All NIDA PA's and RFA's are reviewed to include research priorities related to minorities, women and gender. NIDA has developed a Program Announcement encouraging Drug Abuse Treatment and Services Research for Women and Pregnant Women.

Recently NIDA has developed a Minority Clinical and Services Research Program Announcement. The purpose of this initiative is to stimulate clinical and services drug abuse research on minority populations, including African-Americans, Hispanics, Native Americans, and other ethnic, racial or cultural minority groups.

NIDA has launched the Behavioral Therapies Development Program as one of its major research priorities to parallel the Medications Development Program. Almost all clinical trials include women and many include gender analyses. A number of clinical trials are investigating the efficacy of cognitive, behavioral and pharmacological therapies for drug dependent women. Investigators are encouraged to develop and test new and gender modified behavioral therapies for women and to conduct studies that will improve the integration of behavioral and pharmacotherapies for drug abusing and drug dependent women. NIDA has developed an Addendum to the Behavioral Therapies Development program which encourages AIDS risk behavior instrument development and the development and testing of HIV/AIDS behavioral risk reduction strategies for women and minorities.

To enhance enrollment of women and minorities in clinical trials NIDA has provided supplemental awards to grants. NIDA has supported several Workshops, Symposia, Conferences to encourage more research on women and gender issues.

A NIDA Research Monograph entitled "Treatment for Drug-Exposed Women and Their Children: Advances in Research Methodology" will be published soon. The contents were developed by NIDA-supported "Perinatal-20 Treatment Research Demonstration Program" investigators and reflect their shared experience, skill, and knowledge gained through the conduct of twenty challenging clinical studies.

AIDS/HIV AND DRUG USE

Mr. Stokes: How are advances in drug addiction research impacting the HIV/AIDS epidemic? Please be as specific as possible.

Dr. Leshner: Since AIDS was first identified in 1981, the disease has brought death and widespread physical and social devastation to people and nations worldwide. An estimated one million Americans today are infected with HIV, the human immunodeficiency virus, which causes AIDS; as many as 17 million people are infected worldwide. According to the Centers for Disease Control and Prevention (CDC), 470,288 cases of full-blown AIDS were reported in this country through the end of June 1995. Of these, approximately 60 percent have died. The critical connection between drugs and AIDS has become increasingly evident. As of June 1995, approximately 37 percent of all AIDS cases reported to the CDC were associated with injection drug use (IDU). Additionally, data from the CDC suggest that the majority of new HIV infections are associated with drug use. Groups at extremely high risk of infection include injecting drug users who share needles and other drug-use paraphernalia as well as crack addicts who engage in unprotected sex with multiple partners. Also at high risk are sexual partners and offspring of these drug abusers.

NIDA's years of experience in developing and implementing drug abuse treatment and outreach programs have enabled the Institute to identify, study, and modify drug-use behaviors that increase HIV transmission risks among people who are in- and out-of-treatment. Importantly, and for some counter-intuitively, NIDA-supported studies have shown repeatedly that people still using drugs intravenously are nonetheless amenable to behavior change strategies. A study conducted in New York City demonstrated that multi-faceted risk reduction programs can produce large and significant and sustained decreases in HIV risk behavior among IDUs, even among those who continue their drug abuse. Among actively injecting addicts admitted for detoxification, the use of potentially contaminated syringes has declined from 51 percent of injections in 1984 to only 7 percent of injections in 1992. Further declines in unsafe injection practices were seen in addicts who participated in syringe exchange programs.

Additional NIDA-supported studies have reinforced these findings. University of Pennsylvania researchers studying heroin addicts in Philadelphia found that out-of-treatment subjects were injecting drugs, sharing needles, visiting shooting galleries, and practicing unsafe sex at significantly higher rates than in-treatment subjects. The study found that the addicts who did not receive treatment had a conversion rate to HIV-positive status that was six times higher than the rate among in-treatment injecting drug users who had been regularly exposed to risk-reduction education, counseling, and other strategies. Although drug treatment remains the preeminent means of reducing HIV risk among drug abusers, it has now been shown that much can be accomplished with addicts not yet able or willing to enter treatment. In San Francisco, a city where over half of all IDUs sampled in recent street settings participated in a syringe exchange program, the mean number of injections dropped from 1.9 to 0.7 per day during a six year period. The mean age of drug injectors increased by six years over this period and there was a decrease in the percentage of new injectors from 3 percent to 1 percent.

As the AIDS epidemic is becoming ever more closely tied to the drug epidemic, NIDA research has shown that behavior change is possible to save lives and other costs to society. The Federal drug investment supports a comprehensive program of demand and supply reduction activities which are directed to the overall goal of reducing illicit drug use and its consequences. These activities support the five goals of the 1996 National Drug Control Strategy which are to: motivate America's youth to reject illegal drugs and substance abuse, increase the safety of America's citizens by substantially reducing drug-related crime and violence, reduce health, welfare, and crime costs resulting from illegal drug use, shield America's air, land, and sea frontiers from the drug threat, and break foreign and domestic drug sources of supply.

GENE REPOSITORY

Mr. Stokes: What is the association between genetic predisposition and the diseases and disorders under the purview of your Institute?

Dr. Leshner: There is no doubt that biological and genetic factors play a role in the development of and continuation of drug abuse and addiction. However, these factors interact in complicated ways with psychological, social and environmental factors which may determine the ultimate drug involvement or avoidance. While there is obviously a relationship between initiation and abuse, the factors which predispose an individual to initiation are to some extent distinct from those which predispose an individual to chronic abuse. In general, initiation of drug use and infrequent drug involvement which neither significantly escalates nor has major negative consequences appears to be more a function of social and peer factors while drug abuse appears to be more a function of biological and psychological processes. Although the genetic relationship to substance abuse can be demonstrated in animals in laboratory controlled conditions, it is more difficult to determine the nature and extent of such a relationship in humans in natural settings. However, the nature of that influence has not been determined although it is likely that the magnitude of the contribution is less substantial than was previously hypothesized. Further, such findings are complicated because parents contribute to their children both genetically and in terms of social and environmental factors.

NIDA has recently announced an initiative to expand research on human neuroscience which includes behavioral and molecular genetics studies in humans. While NIDA has supported several programs of population genetics delineating the interaction of genetic and environmental influences on drug abuse, the technology in genetic mapping and the great strides in the Human Genome Project have enabled a closer look at the molecular genetic level. The genetic predisposition of drug abuse is especially difficult (as, for example, compared to Huntington's Disease or others with succinct symptoms) because of its multi-etiological and complex behavior.

An example of results from one family study where substance abusers were interviewed (Merikangas, Rounsaville, & Prusoff, 1990) was that co-morbidity for alcohol abuse, antisocial personality disorder, and depression (but not anxiety disorders) were elevated in siblings who were also substance abusers compared to siblings who were not substance abusers, it is likely that one condition (genetically-related) potentiated a risk in the other.

This kind of result was found in an adoption study where subjects were adoptees whose parents had a history of substance abuse. It was found (Caoret, 1986) that presence of drug abuse in the adoptee was significantly associated with alcohol abuse in the *biologic* parent, and co-morbid diagnosis of antisocial behavior in the adoptee, but not significantly related to the environmental influence of substance abuse in the adoptive parent. Similarly in twin studies (Pickens et al. 1991) the concordance was significantly higher in monozygotic twins who share all their genes compared to dizygotic twins who share only half.

Results from molecular genetics are just now beginning to emerge from our grantees. The strategy has been to determine the genetic predisposition to behaviors or conditions that increase substance abuse. This theory has recently been described by one of our grantees and others as a *reward deficiency syndrome* that is associated with certain cumulative mutations of particular genes. Such genes are involved in the specific brain mechanisms that underlie the brain reward system. For example, it was recently reported that the severity of attention-deficit disorder, conduct disorder, and substance abuse progressively increased from individuals carrying none of the affected genes to those carrying three of the genes under study (Comings et al., 1996). More work is in progress and new projects have been started this fiscal year. As new molecular genetic techniques and methodologies are developed, more tools are provided to study this complex behavior. These tools will help sort out the genetic components from this multi-etiological disease from the environmental and psychological components.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: For the disorders that are under the purview of your Institute, where do we stand today with respect to closing the gap in minority health, specifically what progress do you have to report to the subcommittee this year? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Leshner: Progress we have made over the last year is presented below.

Effective AIDS Prevention with Drug-Dependent African American Women

From the study: A Culturally-Sensitive Education Program to Promote Changes in AIDS High-Risk Behaviors in African-American Drug-Dependent Women, - Ruth Harris, Ph.D., R.N.

The purpose of this study was to test the effectiveness of a culturally-sensitive AIDS education intervention for African-American women who were methadone-dependent clients at four urban treatment centers. Two hundred four women completed the pretest and randomly assigned to treatment and control groups. The treatment consisted of small groups (6-10 women) meeting with two experienced nurse counselors over a period of 16 weeks. This intervention was designed to increase self-esteem, reduce high risk sexual behavior, and increase the women's capability to be effective community change agents. A total 130 women completed all phases of the study, including longitudinal posttest at two, four and seven months after enrollment in the study.

The treatment group exhibited significantly ($p = .029$) more safe sexual behaviors (protected vaginal, oral and anal sex or abstinence) following the experimental program than controls after adjusting for baseline behaviors. No statistically significant differences were observed between the two groups with respect to self-esteem, but statistically significant decreases in depression ($p = .045$) and increased community activism ($p = .005$) were observed for the treatment group as compared to the control group. The data indicate that the Peer Counseling and Leadership Training Program provided culturally tailored, effective messages to African-American drug dependent women that promoted changes in AIDS high-risk behaviors, decreased, and promoted AIDS prevention activities in the community.

No Differences by Ethnicity in Neurobehavioral Functioning Among Cocaine Abusing Adults

Tony L. Strickland, Ph.D., of the Charles R. Drew University of Medicine & Science, presented preliminary findings from his ongoing NIDA-funded research study on neurobehavioral functioning among cocaine abusers of different ethnic backgrounds at the **National Academy of Neuropsychology** Fifteenth Annual Meeting held in San Francisco, CA on November 1-3, 1995. Ninety-seven subjects (32 black females, 16 black females, 26 white females, 13 white males) have been evaluated in accordance with the study protocol, which includes measures of prior drug utilization, psychosocial and neuropsychological functioning, and brain structure and blood flow. Preliminary analyses revealed significant neuropsychological impairment on measures of memory, learning, and attention, but unimpaired functions on measures of language and visuoperceptual functioning. Neuroimaging (MRI) showed no abnormalities except in one subject with a small lesion in the basal ganglia. MRS data showed no significant differences between male and female cocaine users in both the gray and white matter regions. No significant differences were found by ethnicity; however, data indicate that socioeconomic status differences may exist. The overall goal of this work is to assess differences in ethnicity in terms of neuropsychological functioning, brain structure, and blood flow. Data are being collected and analyses are being performed.

Life Skills Training Is Effective Drug Abuse Prevention for Minority Youth; Culturally Appropriate Programs and Ethnic Identity Makes a Difference

Considerable progress has been made in recent years in both increasing our understanding of the causes of drug abuse and the identification of effective prevention approaches for minority populations. Below are key findings from work conducted at Cornell's NIDA-funded prevention research center (Gilbert Botvin, Ph.D.). This center received an ORMH supplement in FY 1993. In broad terms, the research of the center is designed to increase our understanding of the techniques, strategies, and programs capable of reducing the incidence and prevalence of drug abuse with minority youth, to increase current knowledge of the risk and protective factors associated with drug use and abuse, and to improve the skills of drug abuse prevention professionals and educate the general public about drug abuse prevention issues. Selected findings include the following:

- NIDA research (published in the February 12, 1995 issue of JAMA) by center investigators demonstrated the effectiveness of a school-based prevention approach which teaches health

knowledge, anti-drug norms, drug resistance skills along with general personal (coping) skill and social skills. Over a 6-year period, drug use among a cohort of 7th graders from 56 schools was reduced at the end of the 12 grade (N=3597) by up to 44% and polydrug use was reduced by up to 66%.

- Research with 757 inner-city minority (African-American and Hispanic) 7th graders found that this same approach as well as a "culturally focused" version of this prevention approach both significantly reduced intentions to use alcohol and illicit drugs and impacted on mediating variables associated with decreased drug abuse risk.

- Two-year follow-up data with these same youth found that both the generic and culturally focused versions of this prevention approach reduced alcohol use among 9th graders as well as producing changes on the mediating variables associated with nondrug use. Somewhat stronger prevention effects were found for the culturally focused program, indicating that tailoring a prevention program to the target population increases its effectiveness.

- Research from a prevention study with 833 inner-city minority (99%) youth once again found that an approach which teaches a combination of drug resistance skills and general personal and social skills significantly reduces drug use (cigarette smoking, alcohol use, drunkenness, and marijuana use) and polydrug use.

- Epidemiologic data from a dataset of 6,000 largely (80%) minority youth show drug use rates that are the highest overall for Hispanic youth, followed by white youth, and with African-American youth having the lowest rates. However, black males have the highest annual prevalence rates of marijuana use (13.7%) relative to 12.4% for Hispanic youth overall, and 12% for white youth.

- Etiologic research with this population shows that ethnicity (self-identification) moderates psychosocial risk and can buffer against early-stage drug abuse. Youth with low ethnic identity were at increased risk of drug use; high levels of ethnic identity decreased drug use risk by diminishing the adverse effects of peer models, and increasing personal efficacy, self-esteem, and perceived life changes.

- Low personal competence and affective despair (i.e. loneliness and anomie) are important components of drug abuse risk for minority youth, along with peer influence and poor bonding to school and family.

Decreasing Drug Use Among Moderate Using Indian Youth on Reservations; Anger Reduction in Mexican American Youth Leads to Less Deviance

Eugene Oetting, at the Tri-Ethnic Minority Prevention Research Center at Colorado State University is conducting epidemiologic and prevention research with Native American youth. This grant received an ORMH supplement in FY 1994. Data show that drug use among Indian youth who live on reservations has consistently been double that of other U.S. youth. However, since 1980 there have been reductions in use for both white youth and Indian youth who are

moderately involved with drugs. Recently, drug use has increased for white youth who are moderate users, but is still declining among Indian youth who are moderate users; therefore, reducing the disparity in health risks between Native Americans and other Americans. However, there has been no change for white youth and Indian youth who have been heavily involved with drugs. (Frederick Beauvais, Trends in Drug Use Among American Indian Students, 1975-94 With an Adjustment for Dropouts, in press, J. of Public Health).

School discipline problems such as high levels of anger and inability to control anger is linked to academic problems and dropout for Mexican American youth. The center is developing methods for helping Mexican American youth deal effectively with anger so it does not increase problems for them in the school environment. A pilot study tested two alternative methods for controlling anger with 8th grade youth, of whom 22% were Mexican American. One method, cognitive-emotional coping skills training reduced deviance both in and out of school. The number of Mexican American youth in the pilot study was too small to allow separate analysis, however the method worked equivalently for them. (Jerry Deffenbacher, et al., Anger Reduction in Early Adolescents, in press, J. Counseling Psychology.)

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at your institute? How much is included in the FY '97 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Leshner: NIDA's outreach and public education programs target the general public, as well as addiction treatment and prevention practitioners and policy makers. We package and disseminate the results of our research in ways that help these audiences better understand drug abuse and addiction based on what we know from science. The following are some of the most significant of these activities:

NIDA has initiated a series of Town Meetings, to bring the results of our research to the community. These meetings bring together NIDA staff and grantees with representatives of treatment and prevention programs and local community leaders. The meetings serve to inform local leaders of important new research findings that can be useful in their work, to help practitioners and researchers forge relationships, and to give NIDA local level feedback on the usefulness of our research information. The first meeting was conducted in Miami, Florida, on April 1-2, 1996, in cooperation with the University of Miami.

During this year NIDA has had lead responsibility for the implementation of an HHS National Anti-Marijuana Initiative. This includes the production of television and print public service announcements, fact booklets for young teens and their parents, and a video for parents. Distribution of the public service announcements was done in cooperation with the Partnership for a Drug-Free America and the videos and booklets were sent to more than 16,000 school superintendents as a first step in reaching parents and teens with information they need to know

about marijuana.

NIDA Notes is formatted as a 20 page newspaper/magazine and published six times a year. It features stories about new findings of ongoing research. Approximately 20,000 drug abuse practitioners, policy makers, and researchers receive NIDA Notes nationally and abroad.

NIDA's Research Report Series presents the latest research-based information on a number of drugs of abuse, including heroin, cocaine, methamphetamine, and LSD. Each will discuss trends and consequences of use and implications for treatment and prevention. The target audience for this information is educated members of the general public.

NIDA has worked cooperatively with Weekly Reader magazine on two projects targeted at school children and their parents with prevention focused information about drug abuse, addiction, and healthy lifestyles. The first of these projects involved the production of a poster about the dangers of marijuana, with distribution to thousands of classrooms and teachers around the country. The current project is a Parent Supplement to the 1996 Spring/Summer Weekly Reader magazine for the 3rd through 6th grade editions. The Supplement encourages parents to play an active role in their children's lives and engage in discussions about important health-related topics including drug abuse, smoking, nutrition, and exercise. It includes important facts, dispels common myths, provides a quiz for parents to do with their children, and provides useful phone numbers and resources for additional information. The Supplement was sponsored by NIDA and involved collaboration with the Department of Health and Human Services, the National Cancer Institute, the Centers for Disease Control and Prevention, and the President's Council on Physical Fitness and Sports.

Mr. Stokes: In most of the Institutes, these programs are funded in research management and support account, is this the case in your Institute? If so, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are you hurting the most?

Dr. Leshner: NIDA funds outreach and public education programs through its research contract and research management and support (RM&S) mechanism. These programs are considered high priority and will not be affected by funding reductions to the RM&S budget account. Although we have significant progress in outreach programs this past year, there remains critical needs in reaching children and adolescents with credible understandable scientifically based prevention messages.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the Office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Leshner: Support from the ORMH has been invaluable to NIDA's efforts to address the

concern of drug abuse prevention and treatment in minority communities. Drug abuse and its related medical and social diseases are devastating minority communities. Minority populations suffer disproportionately from the consequences of drug abuse and addiction. The financial support from ORMH has been extremely helpful. Moreover, and perhaps, most importantly, the attention and focus of the ORMH keeps in the forefront the importance of the issue of minority health. Its leadership and resources has led to fruitful partnerships and initiatives that we might not have had from other sources.

In May, 1995, with support provided by ORMH in FY 1994 NIDA held a technical assistance meeting for minority investigators around two of its program announcements. In September, 1995 supplemental awards from ORMH were given to NIDA investigators to extend research on Native American issues and to hold four meetings pertaining to various aspects of minority research development. Reports on those activities are provided below.

Technical Assistance Workshop

On May 11-12, 1995 a technical assistance workshop was held to encourage minority scholars to become involved in drug abuse research. Scholars interested in two of NIDA's program announcements, Clinical Research on Human Development and Drug Abuse and Drug Use and Abuse in Minority and Underserved Populations were invited to attend. Twenty-two persons participated as trainees. Funds in the amount of \$50,000 were provided for this activity.

Native American Supplements

In FY 1995 ORMH supported the following grants as part of NIDA's concerns about Native American issues in drug abuse research: Family and Community Drug Abuse Prevention Project, Richard Spoth, Iowa State University (\$75,000); Attrition While Awaiting Drug Treatment, Dennis Donovan, University of Washington (\$40,000); and four sites in the AIDS Cooperative Agreement program (IVDUs Not in Treatment in Alaska, Dennis Fisher, Anchorage, Alaska; Community Outreach Project on AIDS in Southern Arizona, Sally Stevens, Tucson; Multicultural Outreach for HIV/AIDS/Drug Risks, Robert Trotter, Northern Arizona University; and Community AIDS Prevention: A Cross-Over Study, Thomas Crowley, University of Colorado -- total award of \$225,000.)

Four grantees under the NIDA Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research Program were awarded supplements to investigate the effectiveness of AIDS prevention intervention among Native American and Alaska Natives. The grantees have agreed to collaborate in the conduct of the study by adhering to a common design utilizing the same instruments and sharing in the responsibility for data entry and analysis. The sites will also collaborate in reporting findings from the study in referred journals.

The purpose of this multisite study is to determine the most effective recruitment and intervention strategies for reducing HIV transmission among Native American Populations. The study seeks to understand HIV risk behavior affected by cultural factors, risk behavioral patterns, and attitudes toward health promotion among Native Americans in Alaska, Arizona, and

Colorado.

Between October and December 1995 the Principal Investigators and members of their staffs designed and field tested a series of instruments to be used during the study. Data collection began January 1996 across the four sites utilizing a modified version of the Risk Behavior Assessment, supplemented by 5 trailer questionnaires: a mobility assessment, a sexual partners assessment, an acculturation assessment, a consensus model assessment and a network assessment. This battery of instruments are administered over a two week period following the first and second sessions of the NIDA Standard Intervention. A minimum of 15 participants per month who have not been involved in the Cooperative Agreement during the past year will be enrolled in the study across all sites over a 3 to 4 month period. Males are targeted to comprise sixty percent of the individuals enrolled in the study. Finally, each site will conduct four focus groups, two comprised of participants who will be new to the project and two will be comprised of past participants in the Cooperative Agreement. The focus groups will provide data about participants' perception of the effectiveness of the intervention.

Data collection is expected to be completed in May and analyses will begin immediately afterwards. Each grantee is expected to take the lead on writing more than one article and collectively seek to publish the results of the study in a special issue of a journal to be named. No problems have been identified to date.

Meetings Supported by ORMH in FY 1995

1. Factors Contributing to the Development and Retention of African-American Investigators

Funds in the amount of \$50,000 were made available to Ernest Quimby, Ph.D., Howard University, who has a contract with NIDA to provide technical assistance to HBCUs on drug abuse research development. Dr. Quimby has conducted an assessment of research resources and needs among faculty at HBCUs that can be used in discussions of career development for African Americans. Preliminary plans for the meeting have been discussed with a group of African American researchers and scholars convened by NIDA. The meeting will be held in late summer or early fall.

2. Technical Assistance Workshop (to enhance the competitiveness of minority investigators in community-based organizations to conduct drug abuse research)

Funds in the amount of \$55,000 were provided to the two following investigators: \$27,500 to Vernon Shorty, "New Orleans Cooperative Agreement for AIDS Community Outreach and Intervention," Desire Narcotic Rehabilitation Center, and \$27,500 to Rafaela Robles, Ed.D., "Community Support and Integration for Recovering Addicts," Research Institute, Puerto Rico Department of Anti-Addiction Services. Dr. Adelbert Jones, co-investigator with Vernon Shorty and a professor at Florida A&M University, has developed an agenda and recruited persons to attend. The meeting is tentatively scheduled for May, 1996 in New Orleans. Dr. Robles plans to have her meeting in the fall, and has solicited ideas and participation from grantees and other

scholars.

3. Collaborative Research Endeavors (to bring together minority and majority institutions)

Funds in the amount of \$40,000 were provided to Tony Strickland, Ph.D., Charles Drew University and UCLA. Dr. Strickland has scheduled his meeting for October 8-9 in Los Angeles to coincide with the annual national conference on substance abuse, psychopharmacology, psychopathology and culture that he organizes with support from NIDA, NIMH, SAMHSA, and others. He is identifying participants from majority and minority institutions, but has already recruited participation from grantees at Yale and UCLA. Special efforts are being made to include HBCUs and schools in the south and southwest. He has developed a strategy wherein the outcome of the meeting is the establishment of plans for future collaboration; therefore, a great deal of effort is being put into the selection of participants who are committed to collaborations. During the meeting, the facilitation of the collaborative relationship will occur for most of the participants. At the end of the meeting, participants will stay for the conference, October 10-12, and have the opportunity to interact with researchers in the field.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Leshner: The meetings I discussed above are totally funded by ORMH. To effectively reach and involve minority communities as researchers and research participants requires strategies that have to be discussed and developed. ORMH support, solely in some cases, is the avenue for this assistance and leadership.

GENE THERAPY

Mr. Stokes: How critical is gene therapy research to furthering advances in areas of research which are under the purview of your Institute? What disorders would benefit from enhanced research in this area?

Dr. Leshner: We include in our research portfolio studies using molecular genetic techniques to understand the mechanisms of drug action as well as studies looking for the genetic factors underlying vulnerability. While we believe that there is a genetic component of vulnerability to addiction, the fact is that not everyone is vulnerable to addiction, and not everyone is as easily vulnerable to addictions. At the present time we do not yet have a target for gene therapy and have not done any gene therapy research.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

PREVALENCE OF ALCOHOL ABUSE AND DEPENDENCE

Mr. Porter: Your Institute conducts epidemiological research on alcoholism. Can you give us an overview of the percent of the population that meets the criteria for alcohol abuse or dependence? How does this vary by race, sex and age?

Dr. Gordis: The latest data are from the 1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES). The 1-year prevalence of combined alcohol abuse and dependence in the NLAES sample was 7.41 percent, representing 13,760,000 Americans. The following table illustrates the distribution by race, sex and age.

Age	Nonblack Males	Black Males	Total Males	Nonblack Females	Black Females	Total Females	Total
18-29	23.48%	12.33%	22.07%	10.99%	3.32%	9.84%	15.94%
30-44	10.89	8.75	10.65	3.94	4.18	3.98	7.27
45-64	5.61	5.19	5.57	1.45	1.92	1.5	3.47
65+	1.21	0.82	1.18	0.29	0.00	0.27	0.64
Total	11.33	8.25	11.00	4.25	2.88	4.08	7.41

PERCENT OF THE POPULATION IN TREATMENT FOR ALCOHOL ABUSE

Mr. Porter: What percent of this population is presently in treatment for alcohol abuse?

Dr. Gordis: The 1993 National Drug and Alcohol Treatment Utilization Survey (NDATUS) data yield a conservative estimate indicating that approximately 500 out of every 100,000 Americans are in treatment for alcoholism. Due to some inaccuracies in the datasets, this rate is almost certainly an underestimation.

GENETICS

Mr. Porter: For several years, the subcommittee has supported your efforts to conduct research into the genetic underpinnings of alcoholism. Has this research borne any fruit to date?

Dr. Gordis: Vulnerability to alcoholism arises from interactions between genetic and environmental causes. The particular genes conferring vulnerability are unknown, but it is clear that multiple genetic and environmental factors are involved and that individuals may be affected by different factors. Over the past ten years, twin and adoption studies have provided consistent evidence for a heritable vulnerability to alcoholism. Advances in molecular biology have made it feasible to search systematically for individual genes contributing to a person's vulnerability to alcoholism.

Our Cooperative Agreement on the Genetics of Alcoholism (COGA) is a large multi-disciplinary, multi-site collaborative study involving six extramural research study centers. The COGA investigators are searching the entire human genome for genetic markers which are linked (co-transmitted with) alcoholism. In the process of this search, they will be able rigorously to test the involvement of a number of genes hypothesized to contribute to susceptibility to alcoholism, and perhaps discover contributions from other genes not yet suspected of involvement with alcoholism. To date, 7500 interviews of alcoholics and their family members have been conducted; 276 pedigrees have been established and cell lines from 2400 individuals are available for genetic analysis. Biochemical, neurophysiological, and neuropsychological characterization of more than 1500 individuals provided further information to accompany the extensively detailed clinical assessment of the recruited subjects. Genotyping of 990 subjects at more than 160 genetic markers has been achieved and nearly 20,000 genotypes have been entered into the database. The search for linkage has begun and some preliminary results will be reported in June.

COGA was renewed in fiscal year 1995 for five years. Two valuable resources, Cell and Data Repositories, are being established and maintained by COGA. These substantial collections of alcoholic pedigrees and associated data, together with their cell lines will become available to the research community at the end of 1999. They will serve as a critical and unique resource for future studies of the genetics of alcoholism. By that time, phenotypic and genotypic data and biological materials for at least 200 extended families of 3000 individuals will have been accumulated. Another major contribution made by COGA is the development and validation of several diagnostic instruments which are in use internationally.

STUDIES TO IDENTIFY GENES

Mr. Porter: Are we close to identifying genes linked to alcohol craving and tolerance?

Dr. Gordis: To date about 1000 subjects from the COGA families have been genotyped at markers spanning the entire human genome. These genotypic data are being analyzed for linkage to alcoholism as defined by three psychiatric criteria (DSMIII-R, DSM IV, and ICD 10). A public announcement of the first findings is expected in June, 1996, at the Research Society on Alcoholism meeting. Final results from the linkage analysis are expected within 2-3 years.

Alcoholism can be characterized as a disorder of consumption or appetite. The alcoholic cannot control his or her urge to consume alcohol. For many years, investigators postulated a link between eating disorders and alcoholism. However, recent data from the COGA study have shown no connection between the eating disorders of anorexia nervosa and bulimia, and alcoholism.

Through animal studies, we are making progress in our understanding of the inability of the alcoholic to control his or her consumption. For instance, recent studies of alcohol consumption in mice hold great promise. NIAAA just made a 5 year award

to continue mapping genes influencing alcohol consumption in mice. Thus far, several genes have been mapped with great precision. The eventual goal is to identify the genes, clone them, and then identify their products. This research holds much promise.

Mr. Porter: What new research have you planned in this area for 1997?

Dr. Gordis: Animal studies are invaluable for investigations of the inheritance of specific traits. The genetic complement of mice can be manipulated in the laboratory very easily. Controlled breeding may be done and also direct manipulation of the genome itself can be accomplished.

Alcohol researchers are studying animal behaviors that resemble various components of human alcoholic behavior. Consumption of alcohol, appetitive behavior, response to reinforcement, sedative effects, and behavioral activation are some examples. Other examples include the study of the severity of alcohol withdrawal, alcohol-induced hypothermia, and ataxia. Studies in animals will help identify human vulnerability. Identification of human individuals at high genetic risk for alcoholism will require precise identification of genes influencing predisposition. Positional cloning of these genes will be a necessary prerequisite for both genetic diagnosis, and design of interventions based on knowledge of the physiological functions of the products of these genes. Quantitative trait loci (QTL) mapping has enabled researchers to tease out specific alcohol-related genes in mice, which may provide clues on the location of these corresponding genes in humans.

In 1996 NIAAA made several new awards for QTL mapping. In 1997 NIAAA plans to increase the scope of this research to precisely map the location of the genes, isolate them, and identify their protein products. Results from QTL research will provide valuable information for COGA investigators. A good example of such research uses QTL to map genes influencing alcohol consumption in mice. So far, one investigator has mapped several genes with great precision. The eventual goal is to identify the genes, clone them, and then identify their products.

A Program Announcement soliciting applications for QTL mapping of alcohol-related behavioral traits in rodents will soon be released. In 1997 NIAAA will encourage investigators to apply mutagenesis screening to mice to identify alcohol-related behavioral traits. Mutagenesis screening is a complementary approach to QTL mapping that uses chemicals to artificially induce mutations using Mendelian genetic methods.

Replications of COGA data are also being planned. In 1997, NIAAA is planning 3 linkage studies with existing twin/family populations, and 3 new linkage studies with new patient populations.

FETAL ALCOHOL SYNDROME

Mr. Porter: Last year's Senate appropriations report asked you to develop a major behavioral research initiative on fetal alcohol syndrome. What is the state of the science in this area -- do you have the necessary scientific underpinning to begin such an initiative?

Dr. Gordis: The recently completed National Academy of Sciences, Institute of Medicine study was complimentary of NIAAA's ongoing research portfolio. The study recommends establishing an interagency task force to study FAS for which NIAAA would take the lead. The primary recommendations of the IOM report are to increase research in the following areas: relating neurological abnormalities and other neurobiological indices to cognitive and behavioral correlates; examining the adverse developmental effects of prenatal alcohol exposure through expanded clinical research; developing more specific biological markers for diagnosis; and considering the potential role of fetal alcohol exposure, as appropriate, in developmental disability studies in general.

Major strides have been made in our understanding of the physiological processes involved when alcohol interferes with fetal development. The intent of continued research in this area is to find ways of intervening to prevent or treat damage to the fetus once it occurs. Understanding the behavioral components involved in pregnant women's drinking is very complex, however. Identifying which women are at risk is also complex and imprecise. There is still much to be learned about the best methods of altering behavior.

We have studied the effects of warning labels and prevention messages delivered to pregnant women. While warning labels have increased awareness appreciably, the behavioral impacts of warning labels are less certain. Among women in the highest risk category, no reduction in drinking was observed. It is clear that additional efforts are needed to reach the most at-risk women who drink while pregnant. Many of these women may be members of hard to reach populations. One and a half million women of childbearing age still drink at or above the recommended level.

This year, NIAAA is soliciting grant applications with a new program announcement, *Intervention Research to Prevent Alcohol-Related Problems*, to stimulate the design, development, and/or testing of interventions that have the potential to prevent FAS and other alcohol-related problems.

HUMAN BRAIN PROJECT

Mr. Porter: I assume all of your Institutes are involved in the Human Brain Project. Could you describe the objectives of this interdisciplinary project, and which Federal agencies beside NIH are involved?

Dr. Gordis: The Human Brain Project is currently sponsored by 16 Federal organizations, two of which joined in the last year. All of the Institutes that took part in the Brain and Brain Disorders Panel in the Appropriations hearings are participants. NIMH is the lead organization and coordinator for all Federal agencies, NIH institutes, and the university and Federal laboratory supercomputer and information science communities participating in the Human Brain Project. In addition to NIMH, the NIH members include: the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Aging (NIA), the National Institute of Dental Research (NIDR), the National Library of Medicine (NLM), the National Institute of Child Health and Human Development (NICHD), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Neurological Disorders and Stroke (NINDS), the National Cancer Institute (NCI), and the Fogarty International Center (FIC). The other participating federal agencies are: the National Aeronautics and Space Administration (NASA), the Department of Energy (DOE), the Office of Naval Research in the Department of Defense (ONR/DOD), and the National Science Foundation (NSF). Representatives from all of these organizations comprise the Federal Interagency Coordinating Committee on the Human Brain Project (FICC-HBP), which coordinates, funds and steers this effort. The coordinating committee precludes unnecessary duplication of effort across Federal organizations and has significantly enhanced the value of the research supported under this initiative. International interest in the project has been expressed by numerous organizations, and efforts are under way to coordinate such research globally.

The participants are pleased that the House is interested in this important, cross-cutting activity. The Senate requested an update on the progress of this effort (Senate Report 104-145), which is presented in the Congressional Appropriations Committee Report: The Human Brain Project: Forging the New Science of Neuroinformatics.

The long term goal of the Human Brain Project is to provide the means to integrate coherently and comprehensively the vast, diverse and complex data generated by brain and behavioral research. This will increase the efficiency of brain and behavioral research and will accelerate progress in understanding the puzzle of brain function in illness and health. The Human Brain Project supports neuroinformatics research, which knits together the edges of two rapidly advancing and broadly defined areas of science: brain/behavioral science, and informatics, drawing from fields such as information science, computer science, applied mathematics, and engineering. Neuroinformatics is a new area of science, and the Human Brain Project is playing the principal role in its development.

Mr. Porter: Provide a table of the number of institutes and other Federal agencies involved in the Human Brain Project and their financial support.

Dr. Gordis: FY 1995 funding for the Human Brain Project was as follows:

<u>NIH Institutes:</u>	<u>FY 1995 actual funding</u>
NIMH	\$3,166,154
NIDA	\$1,910,999
NIAAA	---
NHLBI	---
NIA	\$173,380
NIDR	---
NLM	\$411,190
NICHHD	\$513,764
NIDCD	\$172,786
NINDS	\$461,340
NCI	---
FIC	---
<u>Other Agencies:</u>	
NASA	\$250,000
DOE	---
ONR/DOD	---
NSF	\$200,000

ALCOHOL AND PREGNANCY

Mr. Porter: Dr. Gordis, what is NIAAA doing to support public education programs about drinking and pregnancy?

Dr. Gordis: In FY 1997, NIAAA plans to implement a public education program targeted to women on drinking and pregnancy. Three low literacy publications are currently being developed -- one for a general audience, one for Hispanic women, and one for Native American women. All three publications will be pretested using focus groups to ensure that the intended message is clear and appropriate for the intended audience. As part of the public education program, television and radio public service announcements will be developed.

Mr. Porter: What are you spending on this now and what are your plans for FY 97?

Dr. Gordis: The fiscal year 1997 budget includes approximately \$1,200,000 for these activities.

Mr. Porter: Dr. Gordis, I understand that the congressionally mandated Institute of Medicine report on fetal alcohol syndrome is about to be released. Can you tell me what the report recommends?

Dr. Gordis: The Institute of Medicine study was complimentary of NIAAA's ongoing research portfolio and recommends establishing a task force to study FAS with

NIAAA taking the lead. Primarily the IOM report recommended increasing research to: relate neurological abnormalities and other neurobiological indices to cognitive and behavioral correlates; examine the adverse developmental effects of prenatal alcohol exposure through expanded clinical research; develop more specific biological markers for diagnosis; and consider the potential role of fetal alcohol exposure, as appropriate, in developmental disability studies in general. Many of these priorities are currently reflected in NIAAA's research portfolio.

MODERATE DRINKING

Mr. Riggs: Dr. Gordis, scientific studies point out that moderate drinking of alcohol has a protective effect against coronary artery disease. What research is your institute planning to do to further investigate this area?

Dr. Gordis: Numerous epidemiologic studies indicate that moderate drinking is associated with a protective effect against coronary artery diseases (CAD). Light to moderate alcohol consumption also reduced mortality in women, but this benefit appears largely confined to women at greater risk for coronary heart disease.

Most of these studies consider the impact of total alcohol consumption over time versus heart disease. NIAAA is encouraging researchers to study the influence of various drinking patterns (e.g., lifelong moderate consumption vs. heavy drinking in youth and abstinence later, vs. beginning consumption later in life) on CAD. In addition, the effects of acute versus chronic alcohol consumption and coronary artery disease needs clarification.

Current understanding of the consequences of moderate alcohol consumption is limited. NIAAA is supporting increased research to determine both beneficial and harmful effects of moderate alcohol consumption. Research issues include: definitions of moderate drinking; the impact of alcohol on coronary artery disease; segments of the population most likely to benefit; the exact cellular and molecular mechanisms of these effects; and risks associated with moderate alcohol consumption. Better understanding of the precise mechanisms by which alcohol is cardioprotective could lead to pharmacologic interventions that provide the same protection without the risks that alcohol poses. Later this year, applications submitted in response to our recent solicitation, "Moderate Alcohol Consumption: Benefits and Risks", will be funded.

RFA ON MODERATE DRINKING

Mr. Riggs: Dr. Gordis, what are the different areas of research stimulated by the recent request for grant applications on moderate drinking?

Dr. Gordis: The Institute has received 62 applications in response to its recent solicitation for proposals to study the effects of moderate alcohol consumption. A broad range of research topics have been proposed by the applicants. They include the effects of alcohol on: the health of the elderly, women, working adults; blood lipids and lipoproteins; antioxidants and wine components; breast cancer; atherosclerosis; blood vessels and nitric oxide; liver, heart and bone tissue; interactions with prescription medications; estrogen status and replacement therapy; blood flow in the brain; hypertension and stroke; osteoporosis; and immune system functioning. These applications will soon be reviewed for scientific merit. Decisions regarding which applications to support will be based on scientific merit and program balance.

Mr. Riggs: Dr. Gordis, newly emerging research points out that the beneficial effect of moderate drinking is partly related to the presence of antioxidants in wine. Will you be authorizing research in this area?

Dr. Gordis: Research proposals concerning the antioxidant properties of wine have been submitted in response to our solicitation. These applications will soon be reviewed for scientific merit. Decisions regarding which applications to support will be based on scientific merit and program balance.

Mr. Riggs: Dr. Gordis, I have been told that research studies point out that wine is a much higher source of antioxidants than e.g. grape juice and that these antioxidants are much more effective in the presence of ethyl alcohol. Do you think this should be further investigated?

Dr. Gordis: Yes, this research merits further study because there is controversy in the field regarding the efficacy of orally administered antioxidants. Not all antioxidants are absorbed from the intestinal tract after drinking in a dose sufficient to mimic the results obtained from chemical tests run in the laboratory.

Mr. Riggs: Dr. Gordis, scientific reports were brought to my attention associating moderate drinking with reduced risk for a host of disease conditions including arthritis, diabetes and osteoporosis. Do you agree that research on the effects of moderate drinking should explore these important areas?

Dr. Gordis: Yes, I do. To learn more about these diseases, atherosclerosis and others, we need research that helps us understand the specific cellular and molecular effects of moderate alcohol consumption on these disease processes. Research proposals concerning these areas have been submitted in response to our solicitation. These applications will soon be reviewed for scientific merit. Decisions regarding which applications to support will be based on scientific merit and program balance.

BENEFITS AND RISKS

Mr. Riggs: Dr. Gordis, I have also heard about a new Harvard University study finding that kidney stone formation was especially reduced in wine consumers. Will you support studies on moderate wine & alcohol consumption and the digestive tract?

Dr. Gordis: A recently published epidemiologic study on beverage use and the risk of kidney stones has shown that the risk of stone recurrence was decreased by consuming 8 ounces of caffeinated and decaffeinated coffee (10%), tea (14%), beer (21%), and wine (39%). The national dietary guidelines recommend no more than one drink a day for most women, and no more than two drinks a day for most men. A standard drink of wine is 5 ounces. This means that for wine drinkers to achieve the protective effects, they must consume nearly 1 1/2 glasses of wine. This is greater than the recommended level for women. NIAAA has received some applications proposing studies of the effects of alcohol on the digestive tract. They are under review.

DIETARY GUIDELINES

Mr. Riggs: Dr. Gordis, DHHS and the Department of Agriculture just released the new Dietary Guidelines which emphasize the moderate mealtime alcohol beverage consumption for those who choose to drink. Are you satisfied with the changes that were made regarding alcohol?

Dr. Gordis: Guidelines put forth jointly by the U.S. Department of Agriculture and the U.S. Department of Health and Human Services define moderate drinking as no more than one drink a day for most women, and no more than two drinks a day for most men. A standard drink is generally considered to be 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits.

The guidelines further recommend the following persons should not consume alcohol: women who are pregnant or trying to conceive; people who plan to drive or engage in other activities requiring attention or skill; people taking medication, including over-the-counter medications; recovering alcoholics; and persons under the age of 21.

I would like to emphasize, however, that as soon as a person deviates from these low levels of alcohol consumption, the risks for fetal alcohol effects, for hypertension, for driving accidents, for trauma and all the other problems associated with increased alcohol consumption, increase dramatically. Therefore, a main thrust of our research is to understand what are the trade-offs, what is the risk-benefit analysis for different stages of life and for different populations. The decision to drink should be made between an individual and that individual's physician.

Mr. Riggs: Dr. Gordis, do you think it would be possible to conduct studies that would investigate the health effects of alcohol consumed in conjunction with a meal since it also may increase the absorption of vitamins and minerals. Do you anticipate research that can evaluate this?

Dr. Gordis: Yes, it is certainly possible to conduct studies examining the effects of alcohol on the absorption of vitamins and minerals. However, at this time we have no applications for research in this area.

Mr. Riggs: Dr. Gordis, with all the scientific developments pointing to the practical beneficial effects of moderate alcohol consumption, would you recommend moderate drinking for anyone over 21?

Dr. Gordis: Because individuals vary in their susceptibility to alcohol and in the condition of their health, I believe the decision to drink moderately, or not drink, is best made between the patient and his or her physician.

EXTENT OF THE PROBLEM

Mr. Stokes: For the diseases and disorders that are under the purview of your institute, what is the extent of the problem?

Dr. Gordis: More Americans misuse alcohol than any illegal drug. The economic and social destruction wrought by alcohol abuse and alcoholism in the United States equals or exceeds that associated with other contemporary medical problems. Financial costs reflect only part of the losses, but estimates of the costs to society from alcohol abuse and alcoholism exceed \$98.6 billion each year. Thirty percent of all suicides, 50 percent of all homicides, and 30 percent of all accidental deaths are attributable to alcohol abuse. In the context of current health care resources, it is noteworthy that up to 40 percent of all patients in urban public hospitals have medical conditions resulting from their drinking, regardless of the condition that brought them to the hospital.

MINORITY HEALTH

Mr. Stokes: What progress do you have to report with respect to minority health and the activities underway at the institute?

Dr. Gordis: One of every 4 Americans belongs to a racial or ethnic minority group. The people who comprise these groups, namely African Americans, Hispanic Americans, American Indians and Alaska Natives, and Asian and Pacific Americans, seemingly experience many of the same alcohol-related problems that affect the majority population. NIAAA research has shown that across minority groups, however, alcohol-related problems and costs are unevenly distributed. Evidence indicates that some groups have disproportionately high alcohol consumption rates and related problems; whereas, other groups drink less and experience fewer associated consequences than the majority population. African-American men, for example, are at greater risk than white men for developing alcohol-induced liver and heart disease. In contrast, the Asian/Pacific American population has low rates of alcohol-related problems, and a small percentage of this group is or has been identified as being heavy drinkers. Some, but not all, Native American tribes have high rates of alcoholism and a high incidence of alcohol-related birth defects. Acculturation, degree of assimilation, and community drinking norms also have been shown to strongly influence drinking patterns, for instance among Hispanics.

These examples drawn from previous research illustrate that minorities can differ from one another and from the general population in drinking patterns and problems. NIAAA is investigating the factors underlying such differences. Research is characterizing the causes of alcoholism and its attendant problems in minorities, and defining effective prevention and treatment measures which respond to the needs of these groups. Knowledge gained from this research ultimately will improve the social and physical health of minority populations.

NIAAA has an active research portfolio that is examining the heterogeneity of ethnic populations. Some examples of specific research include longitudinal studies that examine risk factors for specific ethnic groups. Biological, as well as socio-cultural and environmental factors, that may contribute to the development of alcohol problems in specific ethnic populations are being examined. Family interactions, marital accord and peer group influences are being studied. Large scale genetic studies of Native American tribes are examining genetic differences that may explain why some tribes have high rates of alcoholism while others do not. The need for ethnically sensitive treatment is being explored by Project MATCH which has enrolled 20% minority subjects.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your institute?

Dr. Gordis: The NIAAA has taken significant steps to encourage minority participation in our research programs. The following Institute activities address this important goal:

- Administrative Supplements for Underrepresented Minorities
- Program Announcement: Developmental Grants for Collaborative Projects (new effort)
- Research Project and Training Awards to Historically Black Colleges and Universities
- Minority Access to Research Careers (MARC) Program
- Minority Biomedical Research Support (MBRS) Program
- Minority Predoctoral Fellowship Program
- Minority Technical Assistance Workshop - October 1995 (new effort)
- Minority Research Development Workshop - Spring 1996 (new effort)
- Effects of Alcohol on African-American Communities: A Technology Transfer Project (new effort)
- Short-term Student Research Training Awards (to HBCUs)

The NIAAA has been training and recruiting African American scientists through its own and through NIH-wide programs for many years. The goals of these programs are to expand existing alcohol research efforts concerning the problems of ethnic minorities and to enhance and extend the alcohol research activities of minority scientists as young as the high school level. This is accomplished through hands-on experience in the research laboratory or participation in workshops to gain research expertise and technical skills needed to conduct independent research in our field. Our collaborations involve students and faculty at HBCUs as well as minority individuals working at majority institutions.

The Administrative Supplements for Underrepresented Minorities Program is the largest program the Institute utilizes to increase the number of minority investigators in

alcohol research. This program offers support for high school level students through investigator levels to work in established laboratories and gain invaluable research experience.

In addition to these specific programs, the Institute supports several regular research grants in which investigators include ethnic minority members of the study population as collaborators. These individuals may be MDs/PhDs or students seeking additional research experience. Including members of the study population as research collaborators has two advantages. Minority collaborators learn more about alcoholism research and they can advise the principal investigator regarding the cultural sensitivity of the study design.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at your institute?

Dr. Gordis: NIAAA's public education and outreach activities include developing a variety of publications targeted to different audiences such as front line clinicians, the medical and scientific communities, and the general public. NIAAA is currently developing a series of public/patient brochures, providing research-based information on alcohol abuse and alcoholism. Full text of many NIAAA publications, including all publications targeted to the public, are available on NIAAA's World Wide Web site.

NIAAA convened an interdisciplinary working group of alcohol researchers and health professionals to develop **The Physicians' Guide to Helping Patients with Alcohol Problems**. The clinical recommendations in the **Guide** are based on the findings of more than a decade of research on the health risks associated with alcohol use and on the effectiveness of alcohol screening and intervention methods. This user-friendly 12 page document is only one of many examples of NIAAA's efforts to transfer research findings into clinical practice. To complement the **Guide**, NIAAA also developed a patient flyer entitled, **How to Cut Down on Your Drinking** for physicians to use in counseling their patients.

NIAAA has collaborated with other Institutes and agencies to reach new audiences. For example, NIAAA and the National Highway Traffic Safety Administration developed **A Guide to Sentencing DUI Offenders** for judges and prosecutors to fill a gap in information available to these groups. The 20-page document aids judges and prosecutors in identifying the most effective combination of sanctions and treatment for various offenders. The **Guide** was based on published research in the field. Another example was a pamphlet on alcohol and aging that was developed jointly by NIAAA and the National Institute on Aging.

As part of its outreach efforts, NIAAA displays its publications and databases at more than 15 health-related conferences and workshops annually.

Mr. Stokes: How much is included in the FY '97 budget for the institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Gordis: The fiscal year 1997 budget includes approximately \$1,200,000 for these activities. Comparable amounts for past years were: FY 1996 - \$981,000; FY 1995 - \$1,061,000; FY 1994 - \$1,339,000.

Mr. Stokes: In most of the institutes, these programs are funded in research management and support account, is this the case in your institute?

Dr. Gordis: NIAAA outreach and public education programs are partially supported in the research management and support activity.

Mr. Stokes: If so, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Gordis: Because this is an area of high priority we are working to sustain our outreach activities by developing alternative strategies for disseminating our research findings.

Mr. Stokes: In which outreach areas are you hurting the most?

Dr. Gordis: The printing of important publications and brochures has had to be deferred.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between your institute and the Office of Research on Minority Health?

Dr. Gordis: For several years the NIAAA and the NIH Office for Research on Minority Health have worked together to strengthen research on alcohol abuse and alcoholism among different racial and ethnic populations.

Mr. Stokes: Are there specific projects in your institute that are funded totally by the office, and if so, why and which are they?

Dr. Gordis: One NIAAA project is totally funded by the ORMH..

Mr. Stokes: For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Gordis: The following project is funded by ORMH.

- **Minority Researcher Technical Assistance Workshop**
ORMH Funding: \$49,459
NIAAA Funding: -0-
Proj. Period: 10/15/95-4/30/96
Percent Funding ORMH: 100%

Mr. Stokes: Are there specific projects that are co-funded by the institute and the office, and if so, why and which are they?

Dr. Gordis: In most of the co-funding arrangements NIAAA supports the parent project, while the ORMH funding permits expansion of the original project to further explore health concerns of a minority population.

Mr. Stokes: Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the institute and the office.

Dr. Gordis: The following projects are co-funded by the NIAAA and the Office for Research on Minority Health.

- **Risk Factors for Alcoholism in Native Americans**
ORMH Funding: \$316,329
NIAAA Funding: \$9,304
Proj. Period: 9/26/94-8/31/99
Percent Funding ORMH: 97%
- **FAS Prevention Research in American Indian Communities**
ORMH Funding: \$110,000
NIAAA Funding: \$396,450
Proj. Period: 5/01/95-4/30/98
Percent Funding ORMH: 22%
- **Effects of Alcohol on African-American Communities: A Technology Transfer Project**
ORMH Funding: \$91,760
NIAAA Funding: \$15,000
Proj. Period: FY 1996
Percent Funding ORMH: 86%
- **Alcohol Related Problems Among Filipino Americans**
ORMH Funding: \$112,000
NIAAA Funding: \$190,102
Proj. Period: 9/30/95-8/31/99
Percent Funding ORMH: 37%

- Alcohol Related Social Movements among African Americans
ORMH Funding: \$47,500
NIAAA Funding: 305,731
Proj. Period: 9/01/95-8/31/99
Percent Funding ORMH: 13%
- Phenotypes of Alcoholism Among Native Alaskans
ORMH Funding: \$285,205
NIAAA Funding: \$131,211 (est. FY 1996 award)
Proj. Period: 9/20/94-8/31/99
Percent Funding ORMH: 68%
- Optimizing and Evaluating Alcohol Warnings on TV Ads
ORMH Funding: \$28,500 (Supplement)
NIAAA Funding: \$179,828 (est. FY 1996 award)
Proj. Period: 8/01/95-7/31/99
Percent Funding ORMH: 14%
- Investigation and Verification of High Incidence of Fetal Alcohol Syndrome in South Africa: Implications for the African-American Community
ORMH Funding: \$50,000
NIAAA Funding: \$15,000
Proj. Period: 5/10/96-9/30/96
Percent Funding ORMH: 77%
- The Role of Poor Nutrition in the High Incidence of Fetal Alcohol Syndrome in the African-American Population
ORMH Funding: \$385,000
NIAAA Funding: \$300,000
Project Period: 9/30/96-9/29/98
Percent Funding ORMH: 56%
- Family Transmission and Linkage studies on Alcoholism and Anxiety Disorders Using the Low Voltage Alpha and Monomorphic Alpha EEG (electroencephalogram) Phenotypes
ORMH Funding: \$250,000
NIAAA Funding: \$200,000
Proj. Period: FY 1996-1997
Percent Funding ORMH: 56%

GENE THERAPY

Mr. Stokes: How critical is gene therapy research to furthering advances in areas of research which are under the purview of your institute? What diseases and disorders would benefit from enhanced research in this area?

Dr. Gordis: NIAAA scientists are deeply involved in developing a better understanding of the genetic basis of alcoholism, which is a heterogeneous, genetically complex disorder. It is unclear at this time whether gene therapy will be feasible in alcohol abuse or alcoholism, but it is certainly possible that it may someday be applicable to very specific subtypes. For all disorders under the purview of this Institute, it is premature to pursue gene therapy. Scientists are actively working to elucidate the underpinnings of alcohol abuse and alcoholism. NIAAA researchers are keenly interested in pursuing the subject of genetic vulnerability to organ damage and are proposing this as an area of special emphasis. Investigators in NIAAA's large, multi-disciplinary, multi-site collaborative study are searching the entire human genome for genetic markers which are linked (co-transmitted with) to alcoholism. In this process, they can test rigorously the involvement of a number of genes hypothesized to contribute to susceptibility to alcoholism, and perhaps discover contributions from other genes not now suspected to be involved. Once we have a better understanding of the underlying genetic basis of the disorders encompassed in our mission, we will be in a better position to evaluate the pursuit of gene therapy.

IOM ASSESSMENT

Mr. Stokes: What recommendations did the Institute of Medicine make in their recently completed review of the institute's fetal alcohol syndrome research portfolio and how is your institute responding to these recommendations?

Dr. Gordis: The Institute of Medicine study was complimentary of NIAAA's ongoing research portfolio and recommends establishing a task force to study FAS with NIAAA taking the lead. Primarily, the IOM report recommended increasing research to: relate neurological abnormalities and other neurobiological indices to cognitive and behavioral correlates; examine the adverse developmental effects of prenatal alcohol exposure through expanded clinical research; develop more specific biological markers for diagnosis; and consider the potential role of fetal alcohol exposure, as appropriate, in developmental disability studies in general. Many of these priorities are currently reflected in NIAAA's research portfolio.

OPPORTUNITIES

Mr. Stokes: What are some of the most promising opportunities in basic alcohol research?

Dr. Gordis: Some of the areas which hold the most promise include the study of the function of genes mediating uncontrolled alcohol intake and the identification of critical gene-environment interactions contributing to activation of reward-related genes. Further research employing molecular biology and neuroimaging techniques would examine specific neural circuits to gain insight into the motivational aspects of alcohol seeking behavior. Large differences exist among individuals in terms of incidence and severity of medical complications of alcoholism, such as liver cirrhosis, cardiomyopathy, pancreatitis, and fetal alcohol syndrome. Measuring different responses of genes and gene products to environmental factors or infectious agents would permit more certain

identification of targets for intervention and help interpret the wide variance in individual vulnerability to alcohol-induced injury. Of special interest is understanding the impaired immune system response exhibited by alcoholics who show increased susceptibility to infectious diseases. Further research on alcohol-induced changes in the functions of cytokines, growth factors, estrogens, adrenal corticoids, vitamin D3, calcitonin, and parathyroid hormone will help identify appropriate targets for intervention. Future research will also clarify the relationship between cognitive impairments and brain damage and specific mechanisms altered by chronic alcohol exposure. Important goals in fetal alcohol research include further advances in knowledge of the underlying mechanisms of alcohol-induced teratogenesis that are needed for the prevention of FAS, as well as the improvement of therapeutic intervention for affected individuals.

TREATMENT

Mr. Stokes: Now that naltrexone has been approved by the FDA, what is the next step in the development of medications?

Dr. Gordis: Other medications are also being tested in clinical trials, including serotonin re-uptake inhibitors for alcoholics with collateral major depression, serotonin antagonists for patients with early versus late onset alcoholism, an antidepressant (imipramine) for alcoholics with collateral panic disorder, and an anxiolytic (buspirone in comparison with lithium). Acamprosate, a European compound that acts on GABA and NMDA receptor systems, is being tested in clinical studies throughout Europe with promising results. NIAAA has provided consultation on methodology and design issues and provided our Project MATCH manuals to pharmaceutical companies that plan to initiate clinical trials when acamprosate is approved for clinical investigation in the U.S.

Mr. Stokes: What further studies are needed with naltrexone?

Dr. Gordis: As the first medication approved for alcoholism treatment in 40 years, naltrexone represents a significant step forward. Now, NIAAA-sponsored clinical trials are determining which groups of patients are most responsive to this medication as well as the benefits and side effects of long-term use. These include studies of long-term efficacy, mechanisms of action, patients with concomitant drug dependence, patients with recent liver transplant, comparison with the serotonergic agent nefazadone, and comparison with carbamazepine and lithium. Additionally, clinical trials incorporating behavioral treatment in conjunction with naltrexone hold promise to better indicate which populations will benefit most from naltrexone.

GENETICS OF ALCOHOLISM

Mr. Stokes: You mention in your justification that scientists participating in the cooperative agreement on the genetics of alcoholism (COGA) have collected data from hundreds of people. Can you tell us what you've learned thus far?

Dr. Gordis: Clearly, multiple genetic and environmental factors are involved in vulnerability to alcoholism and individuals may be affected by different factors. COGA

investigators are searching the entire human genome for genetic markers which are linked to (co-transmitted with) alcoholism. To date, 7500 interviews of alcoholics and their family members have been conducted; 276 pedigrees have been established and cell lines from 2400 individuals are available for genetic analysis. Biochemical, neurophysiological, and neuropsychological characterization of more than 1500 individuals provided further information to accompany the extensively detailed clinical assessment of subjects. Two valuable resources, Cell and Data Repositories, are being established and maintained by COGA. These collections of data, together with their cell lines, will become available to the research community at the end of 1999. They will provide a unique and critical resource for further research on the genetics of alcoholism. COGA has also provided a key contribution by developing and validating several diagnostic instruments which are in international use. Although in the past, investigators have postulated a link between eating disorders and alcoholism, recent COGA data have shown no connection between the eating disorders, anorexia nervosa and bulimia, and alcoholism.

Mr. Stokes: What are the next steps?

Dr. Gordis: The next steps are to confirm and enlarge upon COGA's initial findings. Examples of follow-up studies include more precise mapping and cloning of genes initially found by COGA, mapping of new genes, more detailed characterization of subtypes of alcoholism, and elucidation of genetic bases for different alcoholic subtypes. Validation of COGA's genetic findings will require replication in independent studies using subject samples distinct from that of COGA. Some of these studies could be conducted using existing collections of twins and families, while others will require patient populations.

FETAL ALCOHOL SYNDROME (FAS)

Mr. Stokes: I understand that for African-Americans, the risk of FAS is about seven times higher than for whites, even after adjustment for the frequency of maternal alcohol intake, occurrence of chronic alcohol problems, and parity. For some Native American tribes, the incidence also is quite high. What can your institute do to get the message to these populations to stop drinking during pregnancy?

Dr. Gordis: The NIAAA not only continues to disseminate the message that FAS is entirely preventable, but also has made it a priority to target communities that are not being reached adequately by educational efforts. An Institute randomized clinical trial will measure the effectiveness of reducing FAS by combining generalized health education messages on alcohol and pregnancy with specific, individual-focused interventions for pregnant women using alcohol. A new program announcement was released by the NIAAA to stimulate the design, development, and/or testing of interventions that hold the potential to prevent FAS and other alcohol-related problems. In addition, the Institute initiated an NIH-wide interest group involving five other institutes and focussing on the teratology of alcohol. This effort promises significantly improved communication and collaboration on FAS and FAE.

ALCOHOL AND TOBACCO RELATIONSHIP

Mr. Stokes: Is there a relationship between alcohol abuse and tobacco consumption?

Dr. Gordis: Many lines of converging data suggest that alcohol and tobacco consumption are correlated. Smokers consume more alcohol than nonsmokers and alcohol consumers smoke more than nondrinkers. In addition, a large majority of alcoholics smoke heavily and often experience the life-threatening medical consequences of long-term conjoint use, including cardiovascular disease, and cancers of the mouth, larynx, and pharynx.

Co-occurrence of smoking and excessive drinking has important treatment implications. Evidence reveals that the reduction of drinking improves the prospects for successful smoking cessation. Likewise, smoking cessation prior to formal alcoholism treatment appears to improve subsequent drinking outcome.

Mr. Stokes: Has the institute conducted any research in this area?

Dr. Gordis: Yes, the NIAAA supports research on alcohol and tobacco and this topic is an area of special emphasis this year. In the fall of 1995, the NIAAA published a research monograph entitled, "Alcohol and Tobacco: From Basic Science to Clinical Practice." This monograph highlights existing knowledge and identifies future research questions and promising strategies for further study. Important topics include: neurobiologic mechanisms underlying the alcohol/ tobacco interaction; clinical and treatment issues related to alcoholics with nicotine addiction; and public health issues related to alcoholism treatment.

To further explore the relationship between alcohol and tobacco, we issued a Request for Applications (RFA) on "The Role of Tobacco Dependence in Alcoholism Treatment." The RFA elicited a strong response. Forty-one applications are currently under review and several will be funded later this year.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials underway at the institute, and specifically, what can you tell us this year that you could not tell us last year?

Dr. Gordis: The NIAAA supports a balanced portfolio of clinical trials which address pressing questions regarding alcohol abuse and alcoholism. Exciting advances have been made in the development of both medications and behavioral interventions to treat alcoholism. Among the former are naltrexone, nalmefene, and acamprosate. The latter group includes motivationally-based, targeted behavioral and interpersonal support treatments. These two classes of treatment strategies are not competitive. Rather, recent research suggests that pharmacologic agents may be combined effectively with

psychosocial interventions and that their combination further enhances treatment outcome.

NIAAA is conducting research on specific interventions under each category and the two approaches may be linked in other ways. For example, motivational interviewing may enhance patient compliance with a medication regime and a medication-induced decrease of biologically-based urges to drink may increase patient's motivation for psychological treatment.

Several clinical trials of pharmacological treatments for alcoholism are being supported. One examines the efficacy of ondansetron on alcoholism treatment outcome. Experiments with humans have shown that this medication attenuates some alcohol-induced subjective effects including the desire to drink. Researchers aim to evaluate the efficacy of ondansetron in the treatment of alcohol dependent patients. Another project on nalmefene maintenance treatment of alcoholism investigates various aspects of long-term nalmefene treatment. This trial is clearly important, given the high risk of relapse in chronic alcoholism. Another trial is a study of an experimental treatment for alcoholics who have recently had a liver transplant, comparing naltrexone to placebo in a double blind clinical trial. This project also explores whether predictive risk factors associated with relapse in non-transplanted alcoholics also predict relapse in alcoholics who have had liver transplants.

Along slightly different lines, another study is testing the efficacy of Motivational Enhancement Therapy administered prior to treatment for increasing treatment participation and decreasing consumption and problems related to alcohol and other drug use for a sample of adolescents seeking treatment. Besides the evaluation of the effect of Motivational Enhancement Therapy for adolescents (as opposed to adults) this study will contribute new knowledge regarding the influence of pretreatment characteristics on treatment and outcome to guide future intervention efforts.

Another clinical trial focuses on questions regarding brief interventions for injured patients with hazardous drinking events who are treated in a hospital emergency department setting. Institute-supported scientists are also evaluating the feasibility and effectiveness of applying methods for training therapists in clinical trials in order to broaden the repertoire of alcoholism counselors or increase their effectiveness. This research, then, examines whether implementing research-based alcohol treatments in real world settings can improve outcome--a question of considerable significance.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Gordis: The FY 1997 budget request includes \$18.5 million for clinical trials. Comparable amounts for prior years are: \$18 million for FY 1996; \$17 million for FY 1995; and \$20 million for FY 1994.

Mr. Stokes: What is the Institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Gordis: The NIAAA adheres in full to the NIH-wide policy on inclusion of minorities and women in its clinical trials and other clinical studies. Furthermore, prior to the initial promulgation of this policy, NIAAA was aware of the need to enhance the representation of women and minorities in our research. For example, our largest clinical study, Project Match, which was funded before the original guidelines were in place, set goals that would provide an important opportunity to examine gender and racial differences in alcoholism treatment. Specific strategies used in this and other clinical studies include: recruiting in locations where the under-represented populations reside; fully informing patients of the potential risks and benefits as well as our plans and rationale for treatment; highlighting values that are culturally important, such as the family and community benefits; and addressing barriers to participation by providing transportation, child care, and other incentives.

JUSTIFICATION OF THE BUDGET ESTIMATES

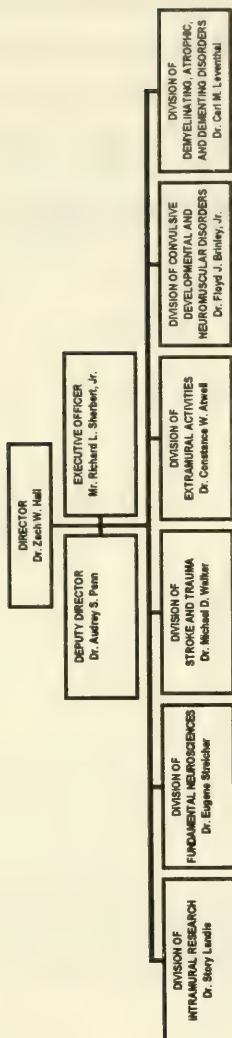
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

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NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

For carrying out section 301 and title IV of the Public Health Service Act with respect to neurological disorders and stroke, \$671,148,000.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Amounts Available for Obligation 1/

	1995 Actual	1996 Appropriation	1997 Estimate
Appropriation.....	\$628,301,000	\$681,534,000	\$671,148,000
Reduction in Accordance with P. L. 103-333.....	-575,000	---	---
Reduction in Accordance with P. L. 104-19.....	-681,000	---	---
Subtotal, adjusted appropriation.....	627,045,000	681,534,000	671,148,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-535,000	---	---
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....	---	-23,807,000	---
Comparative transfer from: Other NIH Institutes for Management Fund Adjustment.....	1,737,000	---	---
Subtotal, adjusted budget authority.....	628,247,000	657,727,000	671,148,000
Unobligated balance lapsing.....	-96,000	---	---
Total obligations.....	628,151,000	657,727,000	671,148,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1995 -- \$4,479,000; FY 1996 -- \$4,400,000 and FY 1997 -- \$4,400,000. Excludes \$96,000 for Royalties in FY 1995. Also excludes funding for HIV activities: FY 1995 - \$22,707,000; FY 1997 - \$23,950,000, included in the Office of AIDS Research, NIH.

Justification

National Institute of Neurological Disorders and Stroke

1995 Actual		1996 Appropriation		1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
651	\$628,247,000	642	\$657,727,000	642	\$671,148,000	-2	+ \$13,421,000

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute of Neurological Disorders and Stroke. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The National Institute of Neurological Disorders and Stroke (NINDS) supports and conducts research and research training on the normal function of the brain, the spinal cord, and the peripheral nerves, and on neurological and neuromuscular disorders. Anyone--newborn, child, teen, or adult--may be faced with the consequences of a birth defect, a genetic disorder, injury, stroke, tumor, or toxic exposure that impairs the ability of the nervous system to function. NINDS research interests include more than 600 neurological disorders--ranging from well-known disorders such as Parkinson's disease and epilepsy to less common disorders such as Batten disease and Friedreich's ataxia--which can be devastating in their impact on patients and families. Examples of major neurological disorders and the number of people living who are currently affected:

Stroke: 3,800,000
 Parkinson's disease: 500,000
 Epilepsy: 2,500,000
 Multiple Sclerosis (MS): 250,000
 Spinal cord injury: 200,000
 Head injury: 1,000,000
 Huntington's disease: 15,000
 Amyotrophic lateral sclerosis (ALS): 13,000-20,000
 Brain tumor: 160,000

Typically, in the quite recent past, the best that could be offered to people with a neurological disorder was a diagnosis and a prognosis of lifelong disability or inevitable deterioration. The outlook has improved with the development of medications for some conditions, such as those for epilepsy and Parkinson's disease, that ameliorate symptoms and enable people to pursue daily activities, even though the medications do little to attack the underlying disease process.

Now, however, we can point to progress in understanding the actual disease mechanisms that are at work and in identifying ways to prevent, to slow, to stop, or even reverse the disease process. For example, in just the last few years the first useful treatments for MS, ALS, spinal cord injury, and acute ischemic stroke have become available. Continued research progress is critical if we are to lessen the burden of neurological disorders, which predominantly are chronic disorders, characterized by deficits in learning, memory, perception, or movement which persist over a long period of time—often a lifetime.

NINDS is joined in this research effort by other institutes and centers of the NIH whose research missions intersect with the neurological sciences. Sleep disorders, chronic pain, diabetic nerve disease, and neurological aspects of AIDS are examples of areas of mutual interest. Collaborative efforts are encouraged to further progress in understanding the brain and its disorders and to maximize the benefit of knowledge and resources.

The NINDS research enterprise is made up of individual investigators and their teams in laboratories and hospitals across the country and in the intramural program of the Institute. Progress in treatment and prevention of neurological disorders depends upon a vital flow of information from a multitude of studies ranging from basic research to understand how a nerve cell functions to epidemiology studies to uncover risk factors for diseases to the testing of new treatments in clinical trials.

NINDS will participate in two NIH special emphasis programs in FY 1997: Biology of Brain Disorders (\$5 million) and Genetics and Medicine (\$2 million). In addition, in recognition of the tremendous opportunities in neurological research, NINDS will increase its support for the training of research investigators in FY 1997.

The following pages contain descriptions of selected areas of research that have emerged with particular promise and opportunity and examples of intramural and extramural efforts that will be pursued by NINDS in FY 1997.

Stroke

Stroke is an interruption in the blood supply of the brain caused by a blocked artery or bleeding blood vessel. Disability and death can result because brain cells deprived of oxygen will die. In stroke research, scientists are making progress on two fronts--prevention and treatment.

For many years, all that could be offered to stroke patients was to "wait and see" how well the patients recovered on their own. Over the past 12 years basic and clinical scientists have been working to understand and exploit the window of opportunity for emergency treatment of stroke. Based on research in animal models and clinical observations, NINDS clinical trial investigators designed an emergency treatment program to work within three hours of the onset of the most common type of stroke, that due to a blood clot blocking a brain artery. In the clinical trial, the drug, t-PA, was administered within three hours of a stroke to dissolve the offending clot and restore blood flow. The results from the clinical trial show that t-PA increases one's chances for an excellent recovery by 30 percent when given within three hours.

The t-PA trial is an important milestone. Just as important, however, this study represents one more step in a systematic, ongoing, NINDS-initiated program against stroke. The carefully crafted clinical and methodologic approaches to evaluate the outcomes of the t-PA trial will guide future attempts to determine the worth of other stroke treatments. The results not only provide dramatic impetus to patient care systems to regard stroke as a treatable emergency with a critical window (hence, the term "brain attack"), but also offer real world models of how community care systems can organize to provide swift high quality care. As these changes are adopted they will facilitate the testing of other potential treatments now in laboratory phases of development, and of course these results are already inspiring fresh ideas.

Over the past several years, NINDS-supported clinical trials have also demonstrated the benefits of medications (aspirin and warfarin) and surgery to prevent stroke in selected patient groups. Clinical trials are continuing that will demonstrate whether these methods can be extended to other patients at risk for stroke. Examples of other research efforts in FY 1997:

- Studies will continue to further identify risk factors for stroke, including differences among various populations, and clarify the mechanisms by which risk factors can lead to stroke.
- Researchers will examine the genetic basis for stroke risk factors and the role of genes in regulating cellular activity that may be involved in recovery from stroke. Animal studies will evaluate gene-based treatments for stroke that may one day be used in humans.
- When stroke occurs, many brain cells are immediately killed, but many more in the surrounding area are in danger of dying off. As cells die, they release substances that kill their neighbors. One important area of research for survivors of stroke involves efforts to understand the cascade of events that damage and kill nerve cells in the minutes and hours following a stroke, so strategies can be developed to protect brain cells from dying and preserve brain function.
- Further research efforts will identify and characterize events that naturally occur after stroke as the brain attempts to establish new connections and remodel itself. These events will be examined in relationship to evidence of functional recovery following a stroke.

- Clinical trials that will continue include studies of ticlopidine, which may have particular benefit in African-American populations to prevent stroke, and estrogen to prevent stroke in post-menopausal women.

Implications for Health: Stroke is the third leading cause of death in the U.S. and the major cause of disability among adults. Estimated costs of stroke total \$30 billion annually for medical treatment, rehabilitation, long-term care, and lost wages. Recent research discoveries are leading the public and health care professionals to change the way they think about stroke. Stroke can now be viewed as a "brain attack" which, like a heart attack, may be prevented or promptly treated. Because more has been learned about the risk factors that lead to stroke, physicians can now better identify an individual patient's risk and determine if that patient will benefit from the known prevention strategies. With inroads into the treatment of stroke, brain damage can be reduced. By learning more about how the brain recovers from stroke, strategies may be devised to improve the quality of life for patients following a stroke.

Common pathways for nerve cell death

Many brain diseases arise from the death or injury of nerve cells. One of the most exciting opportunities in neuroscience research today comes from increasing evidence that points to possible common pathways or mechanisms in disorders as diverse as stroke and acute injury and slow, degenerative diseases such as amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), Parkinson's disease, and Huntington's disease. The pathways, described below, may act alone or in combination to disable and kill nerve cells.

- **Excitotoxicity:** Brain cells communicate with one another by sending tiny amounts of chemical signals (called neurotransmitters) to other cells. These signals may activate (excite) other cells in the brain circuitry or inhibit their activity. In disease or injury brain cells suddenly release large amounts of these signaling molecules which can overstimulate and kill neighboring cells. Investigations will continue to explore the role of excitatory amino acids such as glutamate that have been implicated in epilepsy, stroke, and ALS and to develop methods to inhibit or ameliorate their effects. Already, research progress has led to the testing of new agents in animal models.
- **Oxidative stress:** Highly reactive molecules containing oxygen (commonly referred to as free radicals), released by metabolic reactions, have been implicated in damaging cell components in many neurological diseases including those that are of an acute nature (such as stroke and spinal cord injury) and those that are chronic (such as neuromuscular diseases). Strong evidence for the role of oxidative stress in neurological disorders came with the discovery that one type of ALS is caused by a defect in the body's normal mechanisms to handle free radicals. Research in oxidative stress will include studies of animal models and the potential of antioxidants for therapy.
- **Calcium influx:** Calcium is used inside the nerve cell as a signaling molecule to control enzymes and related cellular processes, but too much calcium in the nerve cell may be harmful. Investigators in stroke and trauma will continue to unravel how excessive calcium contributes to

the complex cascade of events that kill brain cells. In trying to understand how HIV leads to dementia in people with AIDS, scientists will pursue evidence that suggests noxious factors released from HIV-infected cells (called macrophages) trigger excessive influx of calcium.

- **Programmed cell death:** Programmed cell death (apoptosis) is a controlled, orderly process by which the body eliminates unwanted cells. The process occurs normally as a critical factor in the proper development of the nervous system beginning in utero (before birth). Programmed cell death also occurs elsewhere in the body at other times in life, for example, as a mechanism to safely eliminate damaged cells (e.g. by oxidative damage) without harming their neighbors. This is unlike the uncontrolled forms of cell death that can cause cascading damage and inflammation. Programmed cell death may be a final common path for death caused by excitotoxicity, calcium, and oxidative stress, thus bringing all of these themes together and offering new opportunities for therapy of neurological diseases.

Implications for health: By understanding the processes that result in the unwanted death of nerve cells, preventive and therapeutic interventions may be identified for a number of neurological disorders. For example, in Parkinson's disease symptoms of the disease do not become apparent until a large number of nerve cells have already died. By slowing or preventing the process of nerve cell death for PD and other disorders, deficits in memory, language, and motor control may be averted, thus enabling individuals to continue or return to activities at home, work, and school.

Inherited brain disorders and genetic studies

The devastating effects of inherited neurological disorders are clearly evident in disorders as varied as muscular dystrophy and Huntington's disease. Over the past several years, we have witnessed rapid progress in the identification of genes for a number of brain disorders. Approximately 50 genes have now been identified related to diseases of the nervous system; there may be hundreds more. Just in the past year, genes have been identified for ataxia-telangiectasia, Batten disease, and two subtypes of Alzheimer's disease. Unfortunately, finding a gene does not mean a cure is immediately available; it is the first step in a long process to understand the gene and its role in disease. With a gene "in-hand," a framework of investigations can be launched to identify the protein normally made by the gene, discover the function of the protein, determine why an error in the gene leads to functional or structural abnormalities, develop animal models for testing of therapeutic approaches, and improve diagnosis.

One approach to treatment for genetic disease is to find a way to replace the gene product that is missing. NINDS intramural investigators pursued this idea for Gaucher's disease, one of a group of inherited diseases in which the body fails to produce sufficient amount of the enzyme, glucocerebrosidase. The investigators identified the role of the enzyme after eight years of fundamental research, then isolated the enzyme and discovered how to produce it from normal human placental tissue. The enzyme was provided to patients with one form of Gaucher's disease where it was found to be quite beneficial, enabling many to return to normal activities. Researchers are working on ways that may one day lead to a permanent reversal of the defect so continued treatments will not be necessary.

One of the most significant achievements in the past few years has been the discovery that a particular type of genetic defect, known as a trinucleotide repeat, underlies a host of disorders including Huntington's disease, Machado-Joseph disease, spinocerebellar ataxia, and myotonic dystrophy. The defect is due to a three-part sequence of the genetic code that is repeated so many times that the gene's activity is altered. There are differences, however, in how that defect causes disease. For example, in Huntington's disease, NINDS-supported investigators have recently found a protein that binds to the protein made by the HD gene. The longer the expanded repeat in the HD gene, the stronger the protein binds and the earlier a patient develops the disease.

Following are some of the major research avenues to be pursued in FY 1997:

- Research to determine the genetic basis of brain disorders will include major efforts directed at epilepsy and Parkinson's disease. For Parkinson's disease, an intramural study in collaboration with investigators at the National Center for Human Genome Research is underway and extramural projects will be encouraged through a program announcement.
- Continued efforts will examine the phenomenon of the trinucleotide repeat as a mechanism of disease and the disorders in which it occurs. For example, in Huntington's disease, it may be possible that drugs that interfere with the binding between the HD protein and another protein would be useful for treatment.
- The neuronal ceroid lipofuscinoses (NCL) are fatal inherited disorders of the nervous system with onset usually in childhood. In 1995, significant advances were achieved with discovery of the gene for infantile NCL and a different gene for juvenile NCL (Batten disease). This is an example of disorders that are commonly grouped together, but are in fact separate diseases. Work has now been focused on the identification of the biochemical defects, the location of mutations in families, and on better diagnostic tools. In addition, work is being done to develop mouse models of the diseases, and to search for the gene for late infantile NCL.
- Clinical trials of treatment for people with inherited disorders include continued intramural studies of enzyme replacement for Gaucher's disease. Extramurally, a clinical trial is assessing the benefit of bone marrow transplant for several neuronal storage disorders.
- Work will be continued to develop methods to transfer genetically-modified cells where they are needed and to provide for the direct delivery of genes to the nervous system. This approach may have special promise for the treatment of primary brain tumors which are resistant to present therapies.

Implications for Health: Research in neurogenetics offers the promise to find the cause of many disorders, improve diagnosis and, one day, to make available new treatments. The search for "disease" genes is doubly rewarding because of the insights gained into non-inherited forms of the disease (for example, in the case of familial and sporadic Alzheimer's disease), the application of findings in very rare disorders to more common forms of a disease, and new understanding of basic cell functions. For example, the discovery of the gene for ataxia-telangiectasia (AT) is an excellent example of how, increasingly, advances in the neurosciences are rapidly contributing to progress in other fields of biomedical research. In the case of AT, progress in this rare disorder has implications for more prevalent disorders. The AT gene may be a key to understanding signaling and control pathways that are involved in many other

neurological diseases, cancers, and immune disorders. Evidence suggests that people who have one gene for AT, but don't have the disease, may have about a fourfold increased risk of cancer. The relationship between carrier status and the risk of cancer, including breast cancer, can now be more directly explored.

Head and Spinal Cord Injury

One reason for the severity of trauma to the central nervous system is that neurons in the brain and spinal cord fail to regenerate after damage to their axons (the extension of the nerve cell responsible for sending messages to other cells). Through research, scientists seek to understand the processes that result in the death of nerve cells affected by trauma; to discover naturally-occurring factors that may stimulate or inhibit the regrowth of nerve cells; and to identify interventions to save nerve cells before they die or to trigger regeneration. For example, an important finding made in the past year demonstrated that neuronal development patterns, axonal growth, and elongation of axons in mature tissue are regulated not only by the factors surrounding the cells, but also by factors intrinsic to the neurons themselves.

NINDS also supports investigators who are at the forefront of the development of neuroprosthetic devices. These are devices that connect with the nervous system via electrodes to stimulate muscle responses or provide sensory input. Quadriplegic individuals have regained significant hand function using a neural prosthesis developed with NINDS support. This device is now being evaluated in a clinical trial with private funding.

Following are some of the major research avenues to be pursued in FY 1997:

- Further research efforts will be directed at understanding the signals that control the survival, development, guidance, and differentiation of neurons. Research on the intrinsic growth properties of neurons will be especially needed to promote regeneration of long nerve tracts.
- Scientists will seek to devise methods to enhance the survival and growth of neurons through techniques that may involve medications, implantation of cells, and genetic activity.
- Efforts will continue to develop neuroprosthetic devices to assist people with motor and sensory dysfunction.
- In ongoing clinical trials, investigators are evaluating the benefits of hypothermia (low body temperatures) to improve recovery following traumatic brain injury; a medication to prevent post-traumatic seizures; and treatment for spinal cord injury.

Implications for Health: Over 2 million head injuries occur each year. Of that number, approximately 100,000 people die and 500,000 people require hospitalization. Approximately 10,000 people each year experience traumatic spinal cord injury that causes permanent paralysis. Strategies to save and regenerate nerve cells within the injured brain and spinal cord will prevent disability. For people now living with spinal cord injury, research progress offers the opportunity to restore nerve and muscle function. The discovery and development of factors to nourish and stimulate the growth of nerve cells may also contribute to advances in the treatment of other brain disorders such as stroke and ALS.

The Developing Nervous System and its Disorders

Put simply, a healthy nervous system is made up of the right parts in the right place with the right connections. Through research studies in developmental neurobiology, scientists seek to understand how nerve cells grow and stay healthy, become adapted to special functions, migrate to their proper positions, and establish precise and functional contact with other cells. Research progress in developmental neurology benefits from correspondence of findings between vertebrates and simpler organisms. For example, some of the signaling molecules that guide the formation of appropriate connections among brain cells in invertebrates serve the same function in mammals. Following are some of the major research avenues to be pursued in FY 1997:

- **Guidance molecules:** Both short-range (cell-to-cell contact) and long-range (diffusible) signals that guide development have been found in several species. In both cases the signals may act to attract or to repel particular groups of growing axons or migrating cells. Investigations will continue to characterize a family of proteins (netrins) which act as long-range axonal navigation signals. It now appears likely, based on work from several laboratories, that there may be many long-range axonal guidance molecules with different patterns of expression and that growing axons may be differentially responsive to these signals at distinct times in their pathfinding. Research will also continue on short range signaling molecules.
- **Wiring the nervous system:** Apoptosis, or programmed cell death, has become an important topic for studies in the understanding of the formation of the mature nervous system. Investigators will also explore how the process of making connections in the developing nervous system may be influenced by trophic (survival) factors and nerve cell activity.
- **Growth factors:** Efforts will continue to identify and characterize the body's own substances that may act to initiate and control nerve cell growth. Signaling molecules that control survival and growth may one day be used to treat neurodegenerative diseases. For example, neurotrophic factors that either slow the degeneration or augment the function of a patient's residual dopamine-producing nerve cells could be of great importance to the treatment of Parkinson's disease. Glial-derived nerve growth factor (GDNF) and similar compounds will be studied in animal models of neurodegenerative disorders and in grafted tissue.
- **Understanding and preventing developmental defects:** By understanding the normal agents and events involved in the development of the nervous system, researchers gain insight into the inherited disorders of the nervous system and developmental disorders such as cerebral palsy and autism. One area of interest focuses on the benefits and risks associated with specific levels of nutrients. Adverse effects may result from too much or too little, depending on the nutrient. For example, in just the past few years, clinical studies have demonstrated dramatic benefits of supplements of the B vitamin folic acid in reducing the incidence of neural tube defects, such as spina bifida, believed due to low levels of folic acid. In contrast, NINDS-supported investigators have also shown that children born to women who consumed high levels of vitamin A before their seventh week of pregnancy have a higher incidence of birth defects. Vitamin A belongs to a family of compounds that are important signaling molecules controlling early development.

Implications for Health: Research to understand how developmental events take place will help us to understand autism, cerebral palsy, epilepsy, and learning and behavioral problems in children. Scientists may also learn how the signals that control development of the brain can be harnessed to coax useful compensation following nerve injury or stroke, to slow or reverse neurodegenerative diseases, and to facilitate cell transplant and gene therapy strategies for neurological diseases.

Immune mechanisms in neurological disorders and multiple sclerosis

In medicine, a number of disorders are due to an attack by the body's natural defense system on itself—an autoimmune disease. Myasthenia gravis is an example of a neurological disorder resulting from an attack by the immune system against receptors for acetylcholine, the nerve signal that controls muscle contraction. Multiple sclerosis (MS) is suspected to be an autoimmune disease aimed against the myelin sheath surrounding the axon that projects from the nerve cell. In the past year, NINDS grantees have found that one rare type of epilepsy is due to an autoimmune reaction, in which the body's immune system has produced antibodies targeted to one part of a receptor for glutamate, an important signaling molecule. The result is abnormal nerve signaling activity, which results in seizures. There are other important connections between the immune system and the nervous system. For example, in pain research, NINDS grantees have found evidence that endogenous opioids (part of the body's own effort to modulate pain) can be secreted from immune cells to produce analgesia by inhibiting substance-P, the transmitter that appears to relay pain information into the spinal cord. Efforts to be pursued in FY 1997 include:

- Until several years ago, MS was thought to be in remission between acute attacks during the early phase of the disease. Studies done over the past five years in the NINDS intramural program using monthly magnetic resonance imaging to identify new disease activity indicate that in many patients the disease can be active and progressive even during this early stage and when patients appear outwardly to be stable. These findings have provided a new means for monitoring experimental therapies. Moreover, the testing of new therapies can now proceed with a smaller number of patients over a relatively short period of time. Work will also proceed to further examine the changes that occur in the brain affected by MS, for example, to distinguish collections of inflammatory cells from actual tissue damage.
- Basic and clinical studies will continue in an effort to find the cause of multiple sclerosis and evaluate immune-modulating approaches to treatment.
- Hormonal influences on autoimmune disease, reasons for the higher prevalence of MS in women, and the remission of MS during pregnancy will be explored.
- Research will continue to understand interactions between the immune and nervous systems in other conditions.
- The role of endogenous opioids in the control of pain in the periphery (outside of the brain and spinal cord) will be pursued, as well as continuing efforts to understand how the brain and spinal cord process pain signals.

Implications for health: With knowledge of the biological basis of the disease, scientists have important leads to develop new, more specific treatments. Continued efforts to evaluate other agents that interact with the immune system, combined with further progress to understand the cause of MS, may be expected to yield even greater benefit for people with or at risk for MS. Research findings have heightened interest in the possibility that other neurological disorders may have an immunological basis. Novel therapeutics for pain due to inflammatory conditions may be identified and new insights may be gained into the management of pain in immune-compromised patients with AIDS or cancer.

Brain networks and systems

The nervous system connects us to the world by perception (of sights, sound, temperature) by processing information (by thinking, learning, remembering) and then taking action (through speaking, moving). Scientists seek to understand how the nervous system can perform these functions by looking at how nerve cells communicate with each other, how networks within the brain operate, and how the nervous system communicates with other parts of the body such as muscles, immune cells, and the endocrine system. Examples of research activities for FY 1997 that will help us to understand the whole brain include:

- **Brain circuitry:** Continued research to understand brain signaling systems will provide further insights into how the brain works and how defects in brain circuitry lead to certain disorders. For example, NINDS supports a clinical trial to evaluate the benefit of surgery to interrupt brain circuits that may be responsible for some of the motor dysfunction in Parkinson's disease. In other work, researchers can examine the behavior of large populations of neurons through the use of optical and computational technologies.
- **Neural Plasticity:** Even after the brain and spinal cord are established, neural connections may be modified or strengthened as the brain adapts to incoming information from the environment—a process called neural plasticity. Without neural plasticity, normal functions such as learning and remembering would not take place. Additional work will be pursued to determine how these processes take place and pursue evidence that the brain may utilize these mechanisms to make adjustments in response to injury. Derangements in these normal processes will also be examined in relation to disorders such as Alzheimer's disease, epilepsy, and neuropathic pain (which can occur following stroke).
- **Seeing the brain at work:** Brain imaging and recording devices enable investigators to examine the structure and activity of the whole brain, thus providing a "window" into the brain of living patients under normal conditions, when affected by disease, and in response to treatment. For example, the use of brain imaging and recording devices are invaluable in guiding the evaluation of people with epilepsy, especially as candidates for surgery. Studies will continue to explore how humans remember words, speak, or carry out other cognitive and motor functions.
- **Motor Control:** Scientists will continue studies to directly examine how the brain is organized to monitor incoming sensory signals and then respond by controlling muscle

movements, how the body is represented in the brain, how the brain plans and organizes complex movements, and how the brain adapts its representations in response to learning and following brain damage.

Implications for Health: Through research to discover how the brain works, we seek to find new insights into disorders of learning and memory, new understanding of how the brain can reorganize itself after injury, and new information to improve diagnosis, guide rehabilitation, and improve treatments.

Overall Budget Policy

The FY 1997 budget request for the NINDS is \$671,148,000, an increase of \$13,421,000 over the comparable FY 1996 level.

NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 456 competing RPGs, an increase of 3 competing RPGs over FY 1996, and 1,976 total RPGs, an increase of 90 total RPGs over FY 1996.

In FY 1997, the Institute will support 41 centers for \$36,611,000, the same funding level but a decrease of two centers below the FY 1996 comparable level.

Other research grants in FY 1997 will total 229 awards for \$22,439,000, the same level of funding and number of awards as the comparable FY 1996 level. For National Research Service Awards, an estimated 571 research trainees will be supported in FY 1997, an increase of 45 trainees and \$2,137,000 compared with the FY 1996 comparable level.

The research and development contract budget of \$19,230,000 will support 52 contracts, ten contracts and 4626,000 below the FY 1996 comparable level.

The FY 1997 budget request for intramural research is \$76,436,000, the same as the comparable FY 1996 level. The request for research management and support is \$25,258,000, an increase of \$500,000 over the comparable FY 1996 dollar level. The number of FTEs in FY 1997 will be 642, the same as the 642 in FY 1996.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting projects.....	1,193	\$289,024,000	1,372	\$341,562,000	1,441	\$346,988,000
Administrative supplementals.....	(24)	888,000	(40)	1,763,000	(40)	1,799,000
Competing projects:						
Competing renewals.....	268	73,651,000	204	58,095,000	205	52,340,000
New.....	305	61,793,000	243	51,679,000	245	60,354,000
Supplemental.....	9	1,252,000	6	650,000	6	690,000
Subtotal, competing.....	582	136,696,000	453	110,424,000	456	113,384,000
SBIR/STTR.....	63	9,586,000	61	9,147,000	79	12,135,000
Subtotal, research projects.....	1,838	436,194,000	1,886	462,896,000	1,976	474,306,000
Research Centers:						
Specialized/comprehensive ctrs.....	42	38,227,000	43	36,611,000	41	36,611,000
Other Research:						
Research career programs.....	211	17,125,000	206	17,760,000	206	17,760,000
Cooperative clinical research.....	1	981,000	3	2,702,000	3	2,702,000
Minority Biomedical Support.....		125,000		320,000		320,000
Other research related.....	19	2,545,000	20	1,657,000	20	1,657,000
Subtotal, other research.....	231	20,776,000	229	22,439,000	229	22,439,000
Total, research grants.....	2,111	495,197,000	2,158	521,946,000	2,246	533,356,000

Training				
Individual awards				
Noncompeting.....	57	1,537,000	116	3,202,000
Competing.....	125	3,309,000	53	1,897,000
Subtotal, individual.....	182	4,846,000	169	5,099,000
Institutional awards				
Noncompeting.....	270	7,197,000	262	8,174,000
Competing.....	85	2,040,000	95	1,458,000
Subtotal, institutional.....	355	9,237,000	357	9,632,000
Total, training.....	537	14,083,000	526	14,731,000
Research & Development Contracts				
SBIR/STTR.....	46	19,856,000	62	19,856,000
	(7)	(1,753,000)	(17)	(3,000,000)
	FTEs		FTEs	
Intramural Research.....	462	72,346,000	455	76,436,000
Research Management and Support.....	189	26,765,000	187	24,758,000
Total.....	651	628,247,000	642	657,727,000
Clinical Trials.....		(35,390,000)		(37,189,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

FTEs

FTEs

FTEs

FTEs

FTEs

FTEs

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Actual	FTEs	Amount	FTEs	Estimate	FTEs	Amount
Extramural Research:												
Biological Basis research.....	--	\$291,731	--	\$308,063	--	--	\$324,001	--	--	\$352,315	--	+\$9,065
Clinical research.....	--	190,224	--	203,203	--	--	205,135	--	--	217,139	--	+\$3,856
Total extramural		481,955		511,266			529,136			569,454		+12,921
Intramural research.....	503	72,563	474	73,222	462		72,283	455		76,436	455	--
Research management and support.....	206	26,532	195	25,800	189		26,732	187		25,258	187	+\$500
Total, obligations.....	709	581,050	669	610,288	651		628,151	642		671,148	642	+\$13,421
Unobligated balance, lapsing.....		22		66			96	--		--	--	--
Total budget authority.....	709	581,072	669	610,354	651		628,247	642		671,148	642	+\$13,421

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Summary of Changes

1996 Estimated budget authority.....	\$657,727,000
1997 Estimated budget authority.....	<u>671,148,000</u>
Net change.....	+13,421,000

Changes:	1996 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase.....		\$30,078,000		+442,000
b. Annualization of				
Jan. 1996 pay increases.....		30,078,000		+191,000
c. January 1997 pay increases.....		30,078,000		+691,000
d. Payment for centrally furnished services.....		27,735,000		-482,000
e. Service and supply fund increase.....		2,166,000		+48,000
f. Laboratory supplies, materials and other expenses.....		18,623,000		<u>+362,000</u>
Subtotal.....				+1,252,000
2. Research Management & Support				
a. Within grade increase.....		11,666,000		+201,000
b. Annualization of				
Jan. 1996 pay increases.....		11,666,000		+74,000
c. January 1997 pay increases.....		11,666,000		+269,000
d. Payment for centrally furnished services.....		6,069,000		-151,000
e. Service and supply fund increase.....		2,246,000		+49,000
f. Unemployment Compensation and FECF.....		186,000		+8,000
g. Supplies, materials and other expenses.....		6,973,000		<u>+106,000</u>
Subtotal.....				+556,000
Subtotal, Built-in.....				+1,808,000

	1996 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting.....	1,372	343,325,000	+69	+5,462,000
b. Competing.....	453	110,424,000	+3	+2,960,000
c. SBIR/STIR.....	61	9,147,000	+18	+2,988,000
Total.....	1,886	462,896,000	+90	+11,410,000
2. Research centers.....	43	36,611,000	-2	--
3. Other research.....	229	22,439,000	--	--
4. Research training.....	526	14,731,000	+45	+2,137,000
5. Research and development contracts.....	62	19,856,000	-10	-626,000
Subtotal, extramural.....	2,746	556,533,000	+123	+12,921,000
6. Intramural research.....	(455)	76,436,000	(--)	-1,252,000
7. Research management and support.....	(187)	24,758,000	(--)	-56,000
Subtotal, Program.....			--	11,613,000
Total changes.....			--	+13,421,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Authority by Object

	<u>1996</u> <u>Appropriation</u>	<u>1997</u> <u>Estimate</u>	<u>Increase</u> <u>or</u> <u>Decrease</u>
Total compensable workyears:			
Full-time equivalent employment	642	642	---
Full-time equivalent of overtime and holiday hours	3	3	---
Average ES salary	\$110,904	\$116,287	+\$5,383
Average GM/GS grade	9.5	9.5	---
Average GM/GS salary	\$42,825	\$44,904	+\$2,079
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207)	\$79,058	\$82,853	+\$3,795
Average salary of ungraded positions	\$26,771	\$28,070	+\$1,299
Personnel compensation:			
Full-time permanent	\$22,093,000	\$23,118,000	+\$1,025,000
Other than full-time permanent	7,541,000	7,880,000	+339,000
Other personnel compensation	1,301,000	1,360,000	+59,000
Special personal services payments	<u>3,638,000</u>	<u>3,785,000</u>	<u>+147,000</u>
Subtotal, personnel compensation	34,573,000	36,143,000	+1,570,000
Personnel benefits	7,121,000	7,443,000	+322,000
Benefits for former employees	50,000	27,000	-23,000

	1996 Appropriation	1997 Estimate	Increase or Decrease
Travel and transportation of persons	\$1,041,000	\$1,064,000	+\$23,000
Transportation of things	257,000	264,000	+7,000
Rent, communications and utilities:			
Rental payments to other than GSA	237,000	239,000	+2,000
Communications, utilities, and miscellaneous charges	988,000	1,006,000	+18,000
Subtotal, rent, communications & utilities	1,225,000	1,245,000	+20,000
Printing and reproduction	442,000	451,000	+9,000
Other services:			
Consulting Services	301,000	309,000	+8,000
Other Services	1,314,000	863,000	-451,000
Purchases From Govt. Accts.	46,001,000	46,023,000	+22,000
Operations and Maint. of Facilities	2,188,000	1,810,000	- 378,000
R & D Contracts	15,761,000	15,113,000	-648,000
Medical Care	—	—	—
Operations and Maint. of Equip.	1,650,000	1,650,000	—
Subsistence & Support of Persons	—	—	—
Supplies and materials	5,580,000	5,580,000	—
Equipment	3,375,000	2,768,000	-607,000
Grants, subsidies, and contributions	536,677,000	550,224,000	+13,547,000
Insurance Claims	167,000	167,000	—
Interest	4,000	4,000	—
Total	657,727,000	671,148,000	+13,421,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke
Administrative Costs

	1996 Current Estimate	1997 Estimate	Increase or Decrease
Personnel compensation:			
Full-time permanent	\$22,093,000	\$23,118,000	+\$1,025,000
Other than full-time permanent	7,541,000	7,880,000	+339,000
Other personnel compensation	1,301,000	1,360,000	+59,000
Special personal services payments	3,638,000	3,785,000	+147,000
Total personnel compensation.....	34,573,000	36,143,000	+1,570,000
Civilian personnel benefits	7,121,000	7,443,000	+322,000
Benefits to former personnel	50,000	27,000	-23,000
Travel	1,041,000	1,064,000	+23,000
Transportation of things	257,000	264,000	+7,000
Rental payments to other than GSA	237,000	239,000	+2,000
Communications, utilities, and miscellaneous charges	988,000	1,006,000	+18,000
Printing and reproduction	442,000	451,000	+9,000
Other Services:			
Consulting Services.....	301,000	309,000	+8,000
Other services.....	1,314,000	863,000	-451,000
Purchases From Govt. Accounts.....	40,189,000	40,702,000	+513,000
Operation and Maintenance of Facilities.....	2,188,000	1,810,000	-378,000
Operation and Maintenance of Equipment.....	1,650,000	1,650,000	---
Subsistence & Support of Persons.....	---	---	---
Supplies and materials	5,580,000	5,580,000	---
Total.....	95,931,000	97,551,000	+1,620,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

SIGNIFICANT ITEMS IN THE HOUSE AND SENATE APPROPRIATIONS
COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Stroke - ... The House in its report 104-209, page 66 states that the Committee believes that stroke research is important and encourages the NINDS to strengthen its stroke education program and to continue innovative approaches to the diagnosis, treatment, rehabilitation and prevention of stroke as identified in the status report of the Decade of the Brain.

Action Taken or to be Taken

For several years, NINDS has been reporting significant new findings in the prevention of stroke. Now, NINDS research has found the first emergency treatment for stroke in which a clot blocks a major brain artery. Clinical trial results show that the drug, tissue plasminogen activator (t-PA), increases chances for an excellent recovery by at least 30 percent if given within three hours. The trial findings will guide future attempts to develop additional treatments for stroke. Moreover, the trial demonstrated how community health care systems can organize to provide swift high quality care. NINDS is committed to pursuing stroke research opportunities that promise to further alleviate the burden of stroke as well as efforts to inform the public and health care providers about progress against stroke.

Item

Parkinson's disease - ... The House in its report 104-209, page 66 states that recent scientific breakthroughs may open new avenues of understanding and treating Parkinson's and the Committee urges NINDS in the strongest terms to make Parkinson's a very high research priority, enhancing and focusing the Institute's approach to research on the disease and ensuring that funding levels reflect that priority. The Committee acknowledges the importance of the 1995 research planning conference on Parkinson's and encourages NINDS to develop a research plan based on the conference recommendations and report on that plan at the Committee's 1997 hearings.

Action Taken or to be Taken

The FY 1995 conference on Parkinson's disease focused on etiology, various aspects of pathogenesis, and medical and surgical therapies. Several scientific issues stand out from that meeting as areas that warrant greater research attention including genetics, mechanism of neuronal death, standardized criteria for clinical and laboratory diagnosis, growth factors, environmental factors, and mechanisms of movement. Based on the outcomes of the conference, NINDS plans to issue a program announcement calling for applications in the area of genetics of Parkinson's disease. In addition, the intramural program is collaborating with the National Center for Human Genome Research in a genetic study of families with multiple members affected by Parkinson's disease. NINDS is planning with other institutes an initiative on mechanisms of neuronal death and injury. NINDS expects to pursue additional efforts in FY 1997.

Item

Lou Gehrig's Disease - [Amyotrophic lateral sclerosis (ALS)] - ... The House in its report 104-209, page 66 states that the first real finding of a cause of the disease recently occurred with the identification of a gene defect linked to some cases of familial ALS. But more work needs to be done to capitalize on these recent developments in order to successfully treat and cure this disease. The Committee encourages NINDS to maintain its commitment to brain research relevant to ALS.

Action Taken or to be Taken

NINDS remains committed to research that improves understanding of ALS and provides insights to treatment. A number of research avenues are being pursued including the study of animal models, the search for other genetic involvement in ALS, and the examination of other factors that may play a role in ALS such as growth factors and cell signaling molecules.

Item

Neurofibromatosis - ... The House in its report 104-209, page 66-67 states that the Committee encourages the Institutes at NIH with NF projects to work together with the extramural research community to develop a coordinated plan to move this research forward. The Committee encourages NIH in managing this effort to support a variety of collaborative approaches including the possibility of jointly sponsored requests for applications and a NIH-wide consensus conference to bring together experts from throughout the world to make recommendations on research opportunities and priorities.

Action Taken or to be Taken

There are now several institutes at the NIH actively involved in studying the neurofibromatoses. These institutes are committed to coordinating scientific initiatives. Areas identified as especially promising include continued search for mutations in the NF1 and NF2 genes, further studies on the proteins encoded by these genes, and continued study of the role of genes as tumor suppressors under normal conditions. Also, an NINDS representative attended the annual meeting of a major NF organization last year and plans to do so this year.

Item

Gaucher's disease - ... The House in its report 104-209, page 67 states that the Committee continues to be interested in research pertaining to Gaucher's disease and encourages the Institute to continue to place priority on research in this disease area.

Action Taken or to be Taken

Several lines of investigation are actively being pursued in research on Gaucher's disease. In the NINDS intramural program, efforts include study of enzyme replacement therapy for type 2 and type 3 Gaucher's disease and fundamental investigations necessary to develop gene therapy.

Item

Dystonia - ... The House in its report 104-209, page 67 states that the Committee encourages NINDS to work closely with other organizations having an interest in dystonia research to collaborate on joint research programs encouraging investigators to study dystonia.

Action Taken or to be Taken

In 1994, results from a research workshop on dystonia were published in *Neurology*. The workshop served to make investigators aware of research needs in dystonia. NINDS also sponsored, together with a voluntary organization, an international workshop on blepharospasm. The results of that workshop will soon be published. NINDS staff will continue to encourage research in dystonia.

Item

Syringomyelia - ... The House in its report 104-209, page 67 states that the Committee recognizes the success of the syringomyelia conference conducted last year, and urges the NIH to pursue the recommendations made by the experts at that symposium. In addition, the Committee urges the NIH to work with patient advocates and with investigators who wish to pursue research in this area.

Action Taken or to be Taken

The workshop on syringomyelia was held in June 1994. A lay summary from that conference is available from NINDS. In addition, a scientific summary will soon be published in *Neurology*. Research directions identified from the conference have been incorporated into a program announcement issued in January 1995 in collaboration with NICHD. In addition, investigators in the NINDS intramural program are examining the pathophysiology of syringomyelia associated with a congenital abnormality of the brain, Chiari I malformation, and have found a surgical approach beneficial for affected patients.

Item

Niemann-Pick disease - ... The House in its report 104-209, page 67 states that the Committee encourages NINDS to enhance its research on isolating the gene that causes Niemann-Pick Type C.

Action Taken or to be Taken

NINDS intramural investigators linked the gene for Type C Niemann-Pick disease to chromosome 18, and are making progress as they continue to narrow the search for the gene itself.

1996 Senate Report LanguageItem

Parkinson's disease - ... The Senate in its report 104-145, page 79 states that the Committee is pleased by reports from the August 1995 Parkinson's research planning conference that indicate strong potential to produce therapeutic and preventive breakthroughs in the near term with effective use of our research investment. The Committee urges the Director to take steps to expand support for research initiatives in

the areas of promise identified at the planning conference, including considering issuance of request for applications to focus research in these areas.

Action Taken or to be Taken

The FY 1995 conference on Parkinson's disease focused on etiology, various aspects of pathogenesis, and medical and surgical therapies. Several scientific issues stand out from that meeting as areas that warrant greater research attention including genetics, mechanism of neuronal death, standardized criteria for clinical and laboratory diagnosis, growth factors, environmental factors, and mechanisms of movement. Based on the outcomes of the conference, NINDS plans to issue a program announcement calling for applications in the area of genetics of Parkinson's disease. In addition, the intramural program is collaborating with the National Center for Human Genome Research in a genetic study of families with multiple members affected by Parkinson's disease. NINDS is planning with other institutes an initiative on mechanisms of neuronal death and injury. NINDS expects to pursue additional efforts in FY 1997.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Authorizing Legislation

	PHS Act / Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Appropriation	1997 Amount Authorized	1997 Budget Request
Research and Investigation.....	Section 301	42 §241	Indefinite	\$642,996,000	Indefinite	\$654,280,000
National Institute of Neurological Disorders and Stroke.....	Sections 457-459 42 §285j		Such sums as necessary		Authorization is pending	
National Research Service Awards.....	Section 487	42 §288	Such sums as necessary	14,731,000	Authorization is pending	16,868,000
Total Budget Authority.....				657,727,000		671,148,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1988	\$423,193,000	\$554,039,000	\$550,172,000	\$534,692,000 1/
1989 2/	557,585,000	557,046,000	477,878,000	567,690,000
1990	493,502,000	495,225,000	498,988,000	495,625,000 3/
1990 Sequester	---	---	---	-5,216,000
1991 4/	512,212,000	545,225,000	555,488,000	541,743,000 5/
1991 Sequester	---	---	---	-7,000
1992	583,355,000	583,355,000	583,386,000	577,938,000 6/
1993	615,190,000	605,100,000	607,100,000	600,078,000 7/
1994	590,065,000	630,650,000	630,650,000	630,650,000
1995 8/	630,443,000	626,471,000	628,801,000	627,726,000 9/
1996	648,255,000 8/	681,534,000 10/	639,152,000 8/	681,534,000 10/
1997	671,148,000 11/			

1/ Includes funds for a reduction of \$174,000 for travel and transportation costs.

2/ The House allowance excludes \$14,210,000 for the unauthorized training programs (National Research Service Awards). The Senate allowance included the budget for NRSAs. It excluded \$93,100,000 for Other Communication Disorders (NIDCD). The appropriation included the budget for the NRSA program and provided \$96,100,000 for the establishment of the proposed new institute, NIDCD.

- 3/ Excludes an enacted administrative reduction of \$1,471,000.
- 4/ The House allowance excluded \$13,016,000 for the unauthorized training programs (National Research Service Awards). The Senate allowance included the budget for NRSAs.
- 5/ Excludes enacted administrative reductions of \$15,121,000.
- 6/ Excludes enacted administrative reductions of \$4,391,000 and an enacted rescission of \$1,049,000.
- 7/ Excludes enacted administrative reductions of \$6,522,000.
- 8/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.
- 9/ Excludes enacted reductions of \$321,000 for procurement, \$33,000 for SLUC, and \$221,000 for the limitation on 1% Bonus Pay.
- 10/ Includes \$23,807,000 for HIV Research Activities.
- 11/ Excludes \$23,950,000 for HIV Research Activities.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director	68	67	67
Division of Fundamental Neurosciences	7	7	7
Division of Stroke and Trauma	9	9	9
Division of Extramural Activities	63	62	62
Division of Convulsive, Developmental, and Neuromuscular Disorders	35	35	35
Division of Demyelinating, Atrophic, and Dementing Disorders	7	7	7
Division of Intramural Research	462	455	455
Total, NINDS	651	642	642

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Average GS/GM Grade

1992.....	9.7
1993.....	9.9
1994.....	9.9
1995.....	9.9
1996.....	9.9
1997.....	9.5

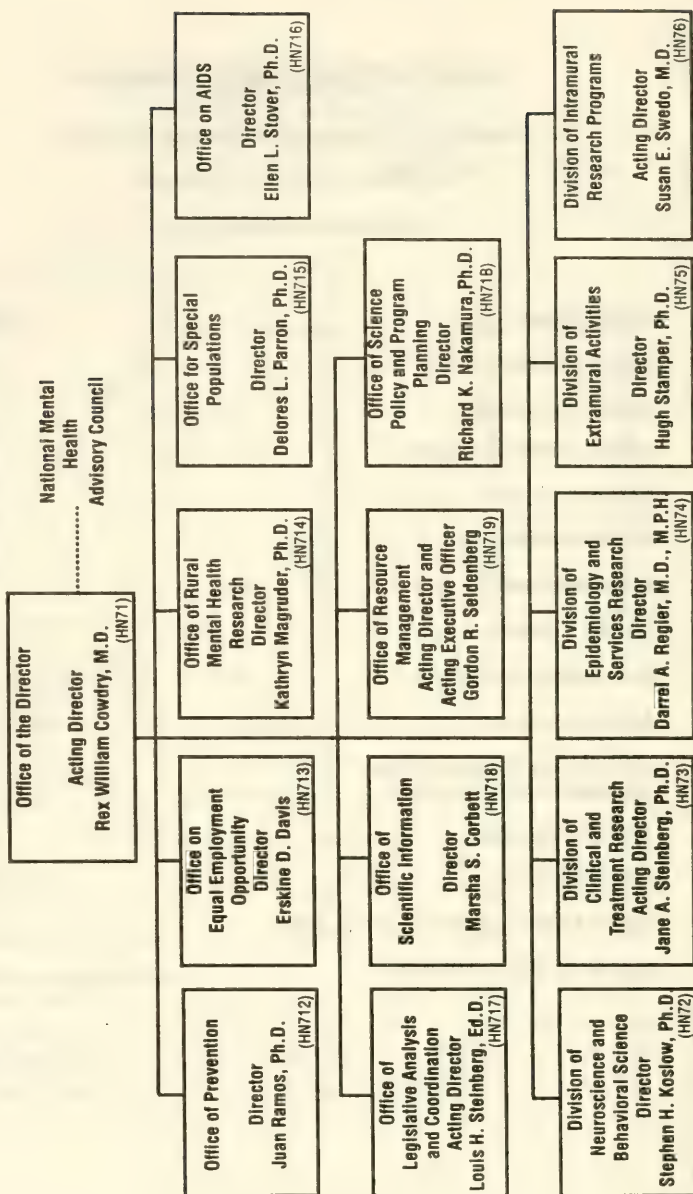
National Institute of Neurological Disorders and Stroke
Program Administration
Detail of End-of-Year Employment

	1995 <u>Actual</u>	1996 <u>Appropriation</u>	1997 <u>Estimate</u>
ES-6.....	1	1	1
ES-5.....	1	1	1
ES-4.....	11	11	11
ES-3.....	1	1	1
ES-2.....	1	1	1
ES-1.....	1	1	1
Subtotal.....	16	16	16
Total - ES Salary.....	\$1,699,900	\$1,774,800	\$1,860,900
GS/GM-15.....	30	30	30
GS/GM-14.....	42	42	42
GS/GM-13.....	45	45	45
GS-12.....	42	42	42
GS-11.....	75	74	74
GS-10.....	2	2	2
GS-9.....	43	42	42
GS-8.....	33	33	33
GS-7.....	67	66	66
GS-6.....	31	31	31
GS-5.....	21	21	21
GS-4.....	29	29	29
GS-3.....	15	15	15
GS-2.....	4	4	4
GS-1.....	1	1	1
Subtotal.....	480	477	477
Grades established by Act of July 1, 1944 (42 U.S.C. 207)			
Director Grade.....	17	16	16
Senior Grade.....	8	9	9
Full Grade.....	11	10	10
Senior Assistant Grade.....	3	3	3
Subtotal.....	39	38	38
Ungraded.....	126	123	123
Total permanent positions.....	504	500	500
Total positions, end of year.....	668	661	661
Total full-time equivalent (FTE) employment, end of year.....	651	642	642
Average ES level.....	3.8	3.8	3.8
Average ES salary.....	\$106,244	\$110,904	\$116,287
Average GS/GM grade.....	9.5	9.5	9.5
Average GS/GM salary.....	\$41,026	\$42,825	\$44,904

JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Institute of Mental Health



NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

For carrying out section 301 and title IV of the Public Health Service Act with respect to mental health, \$578,149,000.

Note -- A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$543,550,000	\$661,328,000	\$578,149,000
Reduction in accordance with P.L. 103-333.....	- 561,000	---	---
Rescission in accordance with P.L. 104-19.....	- 789,000	---	---
Subtotal, Adjusted Appropriation.....	542,200,000	661,328,000	578,149,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	- 464,000	---	---
Comparative transfer to: Office of AIDS Research, NIH for HIV Activities.....	---	-93,556,000	---
Other NIH Institutes for Management Fund adjustment.....	- 863,000	---	---
OD, NIH for accounting services.....	- 286,000	---	---
Fogarty International Center for administration of NIH visiting programs.....	- 17,000	-35,000	---
Subtotal, adjusted budget authority.....	540,570,000	567,737,000	578,149,000
Unobligated balance, lapsing.....	- 27,000	---	---
Total obligations.....	540,543,000	567,737,000	578,149,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1995--\$5,238,000; 1996--\$8,000,000 and 1997 -- \$9,500,000.

Also excludes funding for HIV/AIDS activities: FY 1995--\$89,351,000; FY 1997--\$93,056,000 included in the Office of AIDS Research, NIH.

Note: Excludes \$195,000 in FY 1995 and \$280,000 in FY 1996 for royalties.

Justification

National Institute of Mental Health

FY 1995 Actual		FY 1996 Appropriation		FY 1997 Estimate		Change	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
866	\$541,570,000	847	\$567,737,000	847	\$578,149,000	---	+\$10,412,000

This document provides justification for the FY 1997 NON-AIDS activities of the National Institute of Mental Health. Justification of the NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

The National Institute of Mental Health (NIMH) celebrates 50 years of Federal leadership on mental health and disorder research for the American public. The Institute was authorized in 1946 and established within the National Institutes of Health, where it launched a first-of-a-kind, comprehensive research program on mental illness and health. Throughout its history, NIMH has played a pioneering role in developing the foundations of contemporary neuroscience and behavioral science. The research accomplishments and opportunities presented here reflect NIMH's core mission: supporting and conducting research that seeks to understand, treat, and prevent mental illnesses.

To further its goals, NIMH manages an extensive program of extramural research and research training. The NIMH Intramural Research Program (IRP) contributes to the overall mission of the Institute through its conduct of a comprehensive long-term research program on mental disorders, including the genetic, developmental, environmental, and social factors that determine human behavior and development. The IRP operates laboratories and clinical branches on the campus of the National Institutes of Health, at the Poolesville Animal Facilities, and at the Neuropsychiatric Research Hospital on the campus of Saint Elizabeths Hospital in Washington, D.C. Several hundred active research projects in the basic neurosciences, clinical pharmacology, clinical psychiatry, and behavioral sciences are conducted in these facilities each year.

The Research Management and Support (RMS) activity at NIMH provides staff and resources for the administrative management, financial oversight, and scientific direction of the Institute. RMS funds finance the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions of their program's research grant, contract, and training programs. Other activities include the legislatively mandated NIMH Associate Directors of Special Populations and Prevention and the Office of Rural Mental Health and the Office on AIDS.

STORIES OF DISCOVERY

Understanding the Origins of Schizophrenia

Schizophrenia, the most chronic and disabling of the severe mental disorders, disrupts thought and emotion; shatters young lives; and creates enormous burdens for patients, families, and society. More than two million Americans suffer from schizophrenia each year, filling 100,000 hospital beds on any given day. The total annual cost of schizophrenia to the Nation is estimated at \$32.5 billion. Even with available treatments, most people with schizophrenia continue to suffer chronically or episodically for most of their lives. The disorder causes such agony that one of every 10 patients commits suicide. Multiple lines of NIMH-supported research offer hope for understanding the causes of, and developing ways of treating and preventing, schizophrenia.

Over 30 years, NIMH research has contributed to our understanding of antipsychotic medications, such as chlorpromazine and haloperidol, that can control most positive symptoms in 70 to 85 percent of recent onset schizophrenia. Past NIMH research also has shown us how providing psychosocial therapy for the patient and skills training for family members can reduce the number of patients who will require rehospitalization within two years. Most recently, NIMH researchers have been studying clozapine and risperidone, the first of a new class of antipsychotic medications that is effective in at least a third of those patients whose symptoms do not respond to other medications. Research continues, meanwhile, on pinpointing those parts of the brain's dopamine system that respond to antipsychotic agents and appear to be crucial in the development of the disease.

Numerous twin, family, and adoption studies suggest that genetic factors are important in the etiology of schizophrenia. Evidence suggests that the genetics of schizophrenia is complex, that is, there is not just one gene underlying the vulnerability to the disease, but rather that multiple genes are involved. Detecting a genetic linkage in a complex disorder such as schizophrenia requires large samples. In an NIMH-supported study of 1,408 individuals from 265 schizophrenia pedigrees (families with two or more people suffering from schizophrenia), a potential vulnerability locus for schizophrenia was found on chromosome 6. Final proof for a susceptibility gene will come from identification of the gene and its product.

The findings of several different studies indicate that schizophrenia may be caused by disturbances in brain development before or shortly after birth. These disturbances may be due to genetic or environmental factors with the result that neuronal connections do not mature normally. In human brain development, neurons destined for layers deep within the cortex migrate through several embryonic zones during the first half of gestation. Anatomical findings indicate that the normal pattern of migration of one set of neurons (those containing NADP diaphorase activity) may be altered in the brains of patients with schizophrenia. These findings have led to the determination that another kind of neurons in cortical regions are distributed abnormally in the brain tissue of patients with schizophrenia and may escape the important process of programmed cell death that occurs during normal development. Another group of NIMH-supported researchers used computerized image processing and analysis to examine the

hippocampus region in the brains of patients with severe chronic schizophrenia. This study found that hippocampal neuron size overall was smaller than normal in such patients. The developmental mechanisms that result in smaller neurons in these regions in schizophrenia remain to be determined.

Additional evidence comes from findings that a form of an important protein, called neural cell adhesion molecule (NCAM) is altered in the brain tissues and cerebrospinal fluid (CSF) from patients with schizophrenia. NCAM is a substance involved in embryonic development of the brain and also important in certain areas of the adult brain that continue to undergo synaptic rearrangements. This is called plasticity. Using brain tissues from the NIMH-supported Schizophrenia Brain Bank, scientists found a marked reduction in the embryonic form of NCAM in a subset of cells in the hilus region of the hippocampus, indicating an altered plasticity of this brain structure. NIMH intramural investigators have found significant differences in levels of both NCAM and another cell adhesion protein, L1 antigen, in the CSF of patients with schizophrenia. These findings call for further study to determine the reasons for these observed biological differences between normal individuals and those suffering from schizophrenia.

PROGRESS IN TREATING MANIC-DEPRESSIVE ILLNESS

Approximately 2.5 million adults in the U.S. today (1.2 percent of people over 18) will be diagnosed with manic-depressive illness at some point during their lives. Manic-depressive illness, also known as bipolar disorder, is characterized by episodes of severe depression that alternate intermittently with mania. Manic-depressive illness is a recurring and often life-threatening disorder. Manic-depressive illness severely disrupts lives and causes marked losses of productive capacity. Prior to the introduction of lithium treatment, people with this illness spent, on average, one quarter of their lives institutionalized. When not hospitalized, an estimated one in five patients with manic-depressive illness died by suicide.

Since its beginning, NIMH has conducted and supported basic and clinical research on mental illness, including manic-depressive illness. As a result, we are beginning to understand the biochemical mechanisms involved in manic-depressive illness. Scientists, many of whom were supported by NIMH or who conduct research in the NIMH intramural research program, have also developed an array of effective treatment options. Lithium, effective for approximately 80 percent of patients, is the preferred treatment for the acute mania, depression, and maintenance stages of manic-depressive illness, while a variety of other antidepressant medications are also used for the acute-depression stage.

Lithium and other available treatments allow patients to regain approximately 7 years of life, 10 years of effective major activity, and 9 years of normal health; years which otherwise would have been lost due to the illness. Unfortunately, many persons who suffer from manic-depressive illness do not receive treatment. Because recurring episodes of illness have a cumulative deteriorative effect on a patient's functioning and ability to respond to treatment, it is critically important that patients are diagnosed early and maintained on preventive regimens.

In addition to significant personal burden, manic-depressive illness exacts a heavy economic toll. In 1991, the annual costs to the Nation for manic-depressive illness were estimated to total \$45 billion, including direct costs for inpatient and outpatient care of \$7 billion. However, without effective treatment, these costs would have been much greater. Today, lithium alone reduces the cost burden of this disease by \$7 billion a year, a total of approximately \$145 billion since its introduction in 1970. Of this amount, \$1 billion in savings is attributable to reduced medical care costs and \$6 billion to the restored productivity of manic-depressive illness patients through effective treatment and reduced mortality from suicide. It is noteworthy that annual savings in direct clinical treatment costs alone are more than the total, historical research investment on this illness.

ANNUAL SCIENCE ADVANCES

The Fundamental Knowledge Base of Brain and Behavior Research

Discovering the secrets of the brain and behavior represents some of the most complex challenges to science and medicine and is fundamental to the mission of NIMH. The goals of this work are to discover mechanisms underlying brain function and dysfunction, and to explore the origins of normal and abnormal human behavior. Research serving these goals examines: how individual neurons function and communicate; how memories are formed and learning occurs; how cognition and emotion develop; how genetic and environmental influences shape brain development and function; and how abnormalities in neuronal structure and function can lead to mental illness. In the Decade of the Brain research stands at the brink of unraveling profound mysteries about the human brain and behavior. The explosion of information gleaned from basic neuroscience and behavioral science research in the recent past has presented us with remarkable opportunities to understand how the brain works. Basic behavioral research carries this exploration further by providing the opportunity to understand how behavior unfolds within a person, and within the context of family, society and culture; how cognition and emotion develop; how family and interpersonal processes affect psychological health; and how mental health is an interactive consequence of biology and social experience.

Experience Modulates Cell Death (Apoptosis) NIMH-supported researchers have established a link between two processes important in the shaping and development of the nervous system--programmed cell death (apoptosis) and environmental stimulation. In these studies, apoptosis was caused by changes induced in that part of the brain related to the sense of smell by occluding a nasal passage of rats. Restricting olfactory stimuli also led to increased expression of a gene that protects neurons from apoptosis. These results indicate that apoptosis may be a critical mechanism to the brain's developing olfactory system, and that the gene may regulate neuronal survival. These findings also have a broader significance, which will be the focus of future research, in that they provide additional evidence that gene function can be influenced by the environment; that sensory deprivation during central nervous system development can cause permanent shifts in the nervous system; and that apoptosis is not entirely under genetic control.

Studying Learning and Memory with Brain Imaging NIMH intramural scientists are utilizing brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to describe regions of the brain that are involved in learning and memory. The researchers have begun to explain how experience-related reductions in human recognition memory occur. They are looking to understand the reorganization in the motor cortex -- also called plasticity-- that depends upon life experience and may underlie the acquisition and retention of motor skills. They have described the discrete cortical regions associated with knowledge of color and knowledge of action and how face recognition occurs in the human brain. These studies are invaluable in furthering an understanding of brain mechanisms and physiology involved in the complex functions of learning and memory.

PET Study of Simple Phobia In a positron emission tomographic (PET) study of simple phobia (small animal phobia), NIMH-supported researchers found that exposure to a container with a

feared animal inside resulted in increased regional cerebral blood flow to areas of the brain around the limbic system (the paralimbic system) and to the somatosensory cortex. The paralimbic system is thought to play a critical role in determining the appropriate response to external stimuli. Studies such as this contribute to an understanding of the neuroanatomical and neurobiological bases of phobias.

Quenching Repeated, intermittent administration of a stimulus previously unable to elicit a seizure, can result in the progressive development of seizures in rats. This process is known as "kindling," and is an important tool in the study of epilepsy, long-term neural plasticity and memory, and some psychiatric disorders. Recently, NIMH intramural scientists, were able to restrict the development and expression of kindled seizures with low frequency electrical stimulation. They termed this "quenching." The kindled seizures continued to be controlled for weeks to months, even after the quenching was stopped and daily kindling stimulation reactivated. These results suggest possible clinical applications for epilepsy and other neuropsychiatric disorders.

Brain Changes in PTSD Victims In a magnetic resonance imaging (MRI) study of Vietnam combat veterans with posttraumatic stress disorder (PTSD), scientists found a reduction in the size of the right hippocampus, a brain area associated with learning and memory, in the patients with PTSD compared to control subjects. These brain changes were associated with deficits in short-term verbal memory. The finding that PTSD patients have deficits in memory function is important in treatment strategies. For example, vocational rehabilitation efforts need to take memory function deficits into consideration. Additionally, dysfunction of the hippocampus may explain some of the symptoms seen in patients with PTSD.

Affective Disorders

Over the past several decades, mood disorders have served as a principal focus for scientific research on mental illness, and the results have literally been life-saving. Thirty years ago, one in every five patients with manic-depressive illness (bipolar disorder) died by suicide, as did countless numbers of people who had depression. Today, lithium, antidepressant medications, and supportive psychosocial treatments can treat most, though not all, people suffering from affective disorders. There is hope that the new generation of antidepressants, including the "serotonin reuptake inhibitors," for example Prozac, will prove useful in treating those who do not respond well to traditional antidepressants. In addition, these drugs are proving to be useful probes of the biochemical underpinnings of affective disorders. Modern molecular biology is also providing revolutionary new insights into the biological and genetic roots of depression and mania, which, it is hoped, will provide new treatments and diagnostics for the affective disorders.

New Findings from Genetic Research NIMH research is making great strides in the study of manic-depression, or bipolar disorder. The mode of inheritance of manic-depressive illness does not follow simple Mendelian genetics, rather it is complex. Several recent NIMH-sponsored studies, including studies in the NIMH intramural program, demonstrate two important findings:

1) that there is a linkage of bipolar disorder to chromosome 18, and 2) that there is a parent-of-origin effect that may contribute to the complex inheritance pattern seen in bipolar disorder. Parent-of-origin effects include mitochondrial inheritance--the transmission of genetic traits by mitochondrial DNA, which is contributed exclusively by mothers-- and genomic imprinting--the differential expression of disease alleles depending on the parent of origin. Further studies of mitochondrial DNA and imprinted DNA in bipolar disorder patients will help to clarify the complex genetic patterns of this disorder.

Treatment for Mania The manic episodes of manic-depressive illness are particularly disruptive, with symptoms such as hyperactivity, explosive temper, impaired judgement, delusions, and insomnia. These symptoms often lead to severe functional impairment as manifested by alienation from family and friends, indebtedness, job loss, and divorce. A new randomized, double-blind, placebo-controlled study found that divalproex is an effective treatment for mania. This research is important because it provides an additional treatment option for bipolar patients who do not respond to, or tolerate lithium. NIMH headquarters staff served on the workgroup for the recent development of new "Practice Guidelines for Treatment of Bipolar Disorder," under the auspices of the American Psychiatric Association, to provide guidance to psychiatrists treating patients with bipolar disorder. The purpose of the guidance is to assist the physician with treatment strategies at multiple points in time, since the needs of individual patients vary substantially during the course of this long-term disorder. The guideline includes disease definition, epidemiology, natural history, and treatment principles and alternatives.

Child and Adolescent Mental Health

Research on mental disorders in children and adolescents is a high priority at NIMH. Childhood epitomizes change--more so than any other period in life--and detecting clinically significant mental and behavioral problems against this fluctuating developmental background can be more difficult than diagnosing mental illness in an adult. In the last few years, NIMH has accelerated research activity to begin to clarify the antecedents, course, and outcome of mental disorders in children and adolescents. Many new approaches to diagnosis, treatment, and even prevention are now being developed. In addition, more reliable data on the epidemiology of child and adolescent mental disorders are being collected.

Manic-Depressive Illness NIMH-supported scientists are describing the course of early-onset manic-depressive illness, and the course of relapse and recovery. Findings indicate the importance of educating the families of children with prepubertal-onset major depressive disorder about the possibility for manic symptoms and encouraging early treatment. The search for biological markers of very early onset manic-depressive disorder has begun, and magnetic resonance imaging (MRI) studies suggest that brain structure abnormalities may differentiate children and adolescents with mania from normal children.

Autism Historically, it has been extremely difficult to discover the neuroanatomical abnormalities that underlie the behavioral deficits seen in infantile autism. Now, for the first time, specific neuroanatomical abnormalities have been identified and linked to specific

neurobehavioral deficits. Recent studies have provided clear evidence of functional and structural abnormalities in several brain regions, including the amygdala, hippocampus, septum, mammillary bodies, and the cerebellum. Researchers are also beginning to establish correlations between sites of neural damage and behavioral deficits. For example, abnormalities in information processing are related to structural changes in frontal and parietal cortices of the brain.

Obsessive Compulsive Disorder (OCD) NIMH intramural research has provided important insights into the origins of OCD in children. Researchers have shown that infections with group A β -hemolytic streptococci and other agents may trigger autoimmune responses that cause or exacerbate some cases of childhood OCD and that immunological treatments such as plasmapheresis (a process in which blood is removed and centrifuged, then the packed cells are returned to the patient) and intravenous immunoglobulin can decrease the symptoms of the OCD.

Women's Mental Health Research

The latest data from epidemiological studies continue to show that depression, eating disorders, and anxiety disorders affect women more often than men, and NIMH-funded investigators continue to search for the causes of this gender-based disparity. Though much more research is needed, investigators are generating novel hypotheses that are now propelling research forward. Significant progress has been made, for example, in developing effective therapies for bulimia nervosa. Other research has begun pinpointing many of the factors that can lead to violence against women, a first step in developing interventions to prevent violence. Recent research has highlighted the following:

Interaction of Genes and Environment on Depression in Women If genetic and environmental risk factors are important in the etiology of depression, they interact in complex ways. To study this interaction, NIMH-supported scientists examined how stressful life events and genetic vulnerability influence the risk of onset of major depression in a population-based sample of 2,164 female twins. A number of stressful life events predicted onset of major depression including death of a close relative, assault, serious marital problems, and divorce/breakup. Genetic liability also had a significant impact on risk of onset of depression. Furthermore, the research showed that genetic factors influence the risk of onset of major depression by altering the sensitivity of individuals to the depression-inducing effects of stressful life events.

Eating Disorders Anorexia nervosa is a serious eating disorder that occurs predominately in young women and causes death in 10 percent of patients. NIMH-supported researchers have studied the occurrence and risk factors for this disorder in a population-based sample of female twins. It was determined that the lifetime prevalence of anorexia ranged from 0.51 to 3.70 percent, depending upon the severity of symptoms, and that the mean age of onset was 18-20 years. If one twin suffered from anorexia nervosa, the co-twin was found to be at a significantly higher risk for anorexia nervosa, bulimia nervosa, major depression, and current low weight during her lifetime. These results indicate that anorexia nervosa occurs with a range of symptom

severity, that it is familial in nature, and that it shares familial roots with major depression and bulimia nervosa, another serious eating disorder.

Research on Mental Health Aspects of Breast Cancer Previous NIMH-funded studies showed that supportive group therapy that strengthened the coping skills of breast cancer patients resulted in longer survival. This group of researchers is now looking for the possible psychosocial and biological mechanisms involved, such as better health care utilization and improvement in hormonal and immune functions. It is well known that more than 50 breast cancer survivors experience adverse psychological effects of the breast cancer treatments even three or more years after it ends. A NIMH-supported study has developed a novel conceptualization that such persistent psychological effects of breast cancer treatment as anticipatory nausea and anxiety, intrusive thoughts, nightmares and impairment of vocational, social and sexual functioning may be a manifestation of post-traumatic stress disorder with cancer as a traumatic stressor and classical conditioning as the underlying mechanism of the off-treatment symptoms. The recent discovery of a breast-ovarian cancer susceptibility gene (BCRA1) brings promise of genetic testing for the risk for breast and ovarian cancer. However, before such testing is widely available, it is critically important that its eventual positive and negative psychosocial, psychological and psychophysiological effects be carefully evaluated and appropriate culturally sensitive education and counseling methods be developed and implemented. Such studies have been recently initiated by NIMH and will be actively promoted and supported.

Mental Health of Older People

The challenges in research and treatment of disorders in the elderly are magnified by the heterogeneity of the disorders; by complex medical, neurologic and psychiatric comorbidities; and by changes caused by the normal process of aging. NIMH-supported and conducted research is leading to better understanding of these disorders, to new approaches to treatment and long-term management of symptoms, and to the development of strategies for preventing disease and enhancing the functioning of older patients and their families while reducing disabilities that may be associated with aging. The savings to the national health care system should be enormous. Recent research results include:

Diagnosing Alzheimer's Disease NIMH-supported researchers have found that people who inherit a gene known as apolipoprotein-E4 (APO-E4), associated with Alzheimer's disease (AD), also have reduced brain function before experiencing clinical symptoms of the disease. The researchers identified subjects in their 50s or older, who had mild memory complaints, and had several relatives suffering from AD. Family members who already had AD were also examined. All subjects received positron emission tomography (PET) brain scans and a genetic assessment for APO-E4. The relatives who did not have dementia, but who inherited APO-E4, had lower brain function and greater right-left brain asymmetry in the parietal region of the brain than those without APO-E4. The demented patients showed the greatest reductions in brain function. Thus, the combination of genetic assessment and PET scanning may allow the identification of patients in the early stages of AD, and intervention before permanent brain damage becomes extensive.

Quality and Cost-Effectiveness of Mental Health Services

It is crucial that the remarkable advances made in understanding and treating mental illnesses reach the individuals who suffer from these disorders. This goal can be accomplished through scientific research directed toward finding ways to improve the organization, financing, quality, accessibility, delivery, and cost-effectiveness of mental health services. Recent findings include:

Relationship Between Insurance Coverage and Mental Health Service Use Substantial costs accrue to society and to individuals with mental disorders when mental health services are not used by those who need them. Primary care facilities are overused and the therapies often are not as effective. Many believe that people who do not really need mental health services use them only because they have insurance and that those who are truly needy will get the help regardless of coverage. A new NIMH study, based on data collected from Epidemiologic Catchment Area studies, demonstrates that insurance coverage is strongly associated with getting care. People with mental disorders are less likely to get the mental health services they need without insurance. Thus, lack of insurance coverage reduces utilization as much, or more, among those with a psychiatric disorder as among those without.

Strategies for the Prevention of Mental Illness

Developing the knowledge necessary to prevent specific mental illnesses and behavioral problems and promote mental health would represent the ultimate achievement of biomedical and behavioral research. Such knowledge could also contribute to the prevention of other disorders whose etiology and course are intertwined with mental illnesses and their precursors. The prevention research focus of NIMH thus includes not only mental illnesses, but many other disorders and dysfunctions in which behavioral, social, cultural, and psychological factors are significant contributors to their development. NIMH behavioral and neuroscience research is contributing to understanding heart disease, diabetes and eating disorders, as well as cancer, AIDS and many other diseases involving compromised immunity. Evidence suggests that the progression of these illnesses, especially in their early stages, can be modified by changes in mood and behavior.

Adolescent Transitions Program (ATP) Adolescent problem behaviors often lead to more serious problems, such as drug abuse or criminal behavior in adult years. Intervention strategies currently used to reduce escalation in problem behaviors often aggregate high-risk youths into groups, resulting in increased contact with problem peers, leading to escalation of problem behaviors. NIMH-supported researchers examined intervention strategies and developed the Adolescent Transitions Program (ATP), that engages parents in the program. The researchers found that involving parents, extended families, and other concerned adults in interventions is very important. In addition, it is important that interventions that target high-risk youths occur in their natural context, such as schools.

BENEFITS AND IMPACT OF RESEARCH

The Costs of Mental Illness and the Savings from Research

Misunderstood, often feared, and still stigmatized, the most severe mental illnesses affect some five million American adults, causing inestimable suffering to these patients and their families. But these severely ill patients—suffering from schizophrenia, manic-depressive illness, major depression, panic disorder, and obsessive-compulsive disorder—represent only a part of a broader problem from which few families are immune; for mental disorders can and do occur from childhood to old age, irrespective of gender or race. Overall, one in 10 Americans experience some disability from a diagnosable mental illness in the course of any given year.

While numbers cannot convey the distress accompanying mental disorders, the economic impact can be calculated. Mental disorders cost the United States more than \$150 billion each year for treatment, for the costs of social service and disability payments made to patients, and for lost productivity and premature mortality. Schizophrenia alone costs the Nation some \$32.5 billion annually.

Now, at a time when the costs of the United States' health care system are the subject of extensive national discussion, NIMH's research is demonstrating that diagnosing, treating, and preventing mental illnesses can play a critical role in reducing the Nation's health care bill. Some examples of the notable benefits from NIMH research:

- Lithium therapy for manic-depressive illness is estimated to have saved the U.S. economy more than \$145 billion since 1970.
- Clozapine treatment for schizophrenia, approved by the FDA in 1990, saves an average of \$23,000 in treatment costs per patient annually, largely by reducing the need for hospitalization.
- An analysis conducted for the Senate Appropriations Committee projected that appropriate and timely treatment of severe mental disorders would produce a 10 percent decrease in the use and cost of medical services by people with these illnesses, yielding savings greater than the cost of providing these treatment services.
- A clinical and educational program designed to boost the skills and coping resources of individuals who provide care for an immediate family member with Alzheimer's disease produced savings of over \$17,000 in institutionalization costs per patient and reduced the isolation and fatigue experienced by the caretaker. As families assume an increasingly large role in providing care and assistance to relatives with a mental illness, research is underway to develop similar programs for persons and families struggling with other mental illnesses.
- A program designed to detect and treat depression, reversible delirium, and other mental disorders in elderly patients hospitalized with hip fractures reduced the average hospital stay by two days, with savings of five to eight times the extra cost of evaluating and treating these patients. It is likely that elderly patients admitted to the hospital for other physical ailments could benefit from such programs, with similar cost reductions.

Recent findings that contribute to our knowledge about the costs of mental illness and the benefits of treatment:

Treating Depression is Cost-Effective In a recent study, NIMH-supported scientists examined the overall health care costs associated with depression and anxiety among primary care patients in a large health maintenance organization, HMO. They found that anxiety and depressive disorders are associated with higher health care costs, reflected in higher use of general medical services rather than in higher mental health treatment costs. The authors postulate that substantial cost savings from reduced use of general medical services could result from more intensive primary care mental health treatment. NIMH headquarters staff have published a cost-benefit analysis that indicates that appropriately treating people with depressive disorders is cost effective. The cost calculations provide evidence that the potential monetary benefits outweigh the incremental treatment costs. To identify the greatest opportunity for improving the cost-effectiveness of care for depression, an NIMH-supported study simulated the total costs, health outcomes, and value-of-care consequences of different treatment patterns of depression.

Movement of the PACT Model With NIMH support, in the 1970s a Program for Assertive Community Treatment (PACT) was initiated to create a model for continuous, comprehensive, and highly flexible community care for persons with severe mental illness. New, controlled, NIMH-supported studies of the PACT model have demonstrated a reduced frequency of psychiatric hospitalization and a reduction in the number of inpatient days. In addition, about one-third of the homeless population have severe psychotic disorders such as schizophrenia, severe depression, manic-depressive disorder, or paranoia. By adapting the PACT model to serve homeless persons with severe mental illness, providers were able to give accessible, effective service to homeless people. PACT is the only full-service, cost-effective intervention for persons with severe mental illness that has been tested in multiple, randomized clinical trials in the United States and abroad.

BUDGET POLICY

Key Themes Affecting Management and Administration

Special Emphasis Areas In FY 1997, NIMH plans to spend \$5,000,000 in NIH special emphasis funds for investigator-initiated research on:

- "The Biology of Brain Disorders" (\$3,000,000) NIMH intends to fund research on the genetics of complex disorders, developmental neurobiology, neuroimaging and molecular biology. This initiative would support a wide variety of efforts, ranging from fundamental research in molecular genetics, to animal models of heritable diseases and traits, to the investigation of specific diseases which show complex genetic components. The initiative would include the collection of material from affected families, genotyping to identify the genetic loci linked to the appearance of the disorder, and investigation of the specific biological mechanisms involved.
- "New Preventive Strategies Against Disease" (\$2,000,000) NIMH will focus efforts of prevention of mental disorders in children and adolescents and in women. Other efforts will be centered on the prevention of child abuse and neglect and their sequelae and violence against women. NIMH intends to fund risk factor research to help determine both genetic and environmental risk and protective factors, and focus on prevention of recurrence, deterioration, and morbidity.

Public Private Partnerships

Intramural Research Program (IRP) The IRP continues to develop its growing partnership with industry. Stimulated by the Federal Technology Transfer Act of 1986, the IRP scientists have had a steadily increasing number of collaborations with industry based on their inventions. At the end of FY 1995, nine Cooperative Research and Development Agreements (CRADAs) were active, and two new patents were filed from the thirteen Employee Invention Reports (EIR) submitted. Also five new patents had been issued, bringing the total number of patents issued to NIMH investigators to forty-eight.

NIH Image is an example of an invention created by NIMH intramural scientists, but not patented because Federal employees may not copyright software developed as part of their official duties. From its beginning in 1987, this program has played a major role in revolutionizing the use of image processing in scientific research. *NIH Image* is useful for a wide variety of applications, including analysis of computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) images, receptor binding studies, analysis of electrophoretic gels, and quantitative evaluation of cerebral blood flow, glucose metabolism, or protein synthesis. *NIH Image* is not limited to medical applications and is also widely used in a broad spectrum of other scientific applications involving images, including radar weather maps, satellite terrain maps, microscope pictures, and even artwork. NIMH researchers have distributed it without charge, via electronic bulletin boards and through direct mailings by request. Many hundreds of copies were quickly obtained by scientists and

engineers. The Internet has been used to make each new version of *NIH Image* readily available throughout the United States and in many foreign countries. Currently the program is downloaded from NIMH alone hundreds of times each month. It is also available on numerous CD-ROMs that are published by a variety of technical organizations. Many Federal agencies (including those with critical defense, security, and environmental responsibilities), hundreds of colleges and universities, and numerous private businesses and individuals have benefited greatly from free access to *NIH Image*. Any company or individual is free to incorporate *NIH Image* into their own software, and a great number have done so, including copyrighted software packages sold commercially.

Extramural Research Program The Human Brain Project

NIMH is the lead organization and coordinator for the participation of Federal agencies, NIH institutes, and the university and Federal laboratory supercomputer and information science communities in the Human Brain Project. This initiative is playing the principal role in forging an entirely new area of science called neuroinformatics, which will lead to information solutions that are generalizable to a wide range of scientific uses, including all areas of biology. The Project is currently sponsored by 16 Federal organizations, two of which joined in the last year. International interest in neuroinformatics research has been expressed by numerous organizations, and efforts are under way to coordinate such research globally.

Streamlining and Reinvention The Acting Director of NIMH appointed a committee of Institute employees to study how the Institute's extramural grants are selected for payment and the process for awarding them. The charge to the Committee identified grant selection and award as a core function and critical job element for the Institute's extramural research program. The Committee was asked to view the NIMH grants procedures and databases across current organizational structures and lines of authority. In the context of similar efforts occurring at other National Institutes of Health components, the Committee was asked to find ways to enhance productivity while the Institute's workforce is being reduced. In this spirit of reinvention and Government-wide restructuring, the "Grant Selection and Award Reinvention Committee" met through November 1995. The Committee's report contains important recommendations regarding the Institute's allocation policy, the selection and award process, and automation issues.

Communicating with NIMH The NIMH home page (<http://www.nimh.nih.gov>) serves as a ready source of information for the scientific community. Recently, the home page was used to keep researchers updated concerning issues about general grant review and funding issues, including changes of schedules due to the Government-wide furlough. Ordinarily the homepage provides access to program announcements (PA's) and requests for applications (RFA's); the NIMH Fact Book, covering trends in funding of extramural research; and direct dial telephone numbers for specific staff and offices. The home page also provides information for the general public, including on-line versions of Institute publications about mental illnesses. The Institute also hosts a fax-on-demand system, Mental Health FAX4U. The telephone number is 301/443-5158.

NIMH Budget Policy

The President's appropriation request of \$578,149,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Mental Health during the last five years has been as follows:

	<u>Amount</u>	<u>FTE</u>
1992	\$484,344,000	1029
1993	504,709,000	948
1994	525,757,000	900
1995	541,570,000	866
1996	567,737,000	847

Overall Budget Policy

The FY 1997 budget request for NIMH is \$578,149,000, an increase of \$10,412,000, which is 1.8 percent over the comparable FY 1996 level of \$567,737,000.

In the FY 1997 President's Budget Request, NIMH support for research project grants (RPGs) would increase by 3.4 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997 noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent over FY 1996. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 426 competing RPGs, an increase of 62 competing RPGs over FY 1996, and 1,331 total RPGs, an increase of 32 total RPGs over FY 1996.

The NIMH total request for research centers is \$57,865,000 for 54 centers, which is equal to the number and amount funded in FY 1996. The remaining extramural grant mechanisms are maintained at the FY 1996 funding level, which will support 6 fewer grants. The research training mechanism also maintains FY 1996 funding levels to support 1,198 FTTPs, a decrease of 20 from the FY 1996 FTTP level of 1,218. The request for research contracts is \$12,509,000 which is decrease of \$472,000 to fund 32 contracts, two fewer than in FY 1996.

Funding for the NIMH intramural program is \$87,384,000, which is equal to the level in the FY 1996 Appropriation. FTES are 533 which is the same as in FY 1996.

The research management and support request is \$29,174,000, an increase of \$841,000 over the FY 1996 Appropriation of \$28,333,000. FTES are 315 which is the same as in FY 1996.

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting.....	839	\$203,161,000	880	\$213,817,000	833	\$207,879,000
Administrative supplemental.....	(24)	1,256,000	(24)	1,306,000	(24)	1,332,000
Competing projects:						
Renewal.....	97	21,060,000	101	22,798,000	118	27,246,000
New.....	245	41,188,000	256	44,588,000	300	53,289,000
Supplemental.....	7	640,000	7	693,000	8	828,000
Subtotal, competing.....	349	62,888,000	364	68,079,000	426	81,363,000
SBIR/STTR.....	52	8,095,000	55	8,826,000	72	11,497,000
Subtotal, research projects.....	1,240	275,400,000	1,299	292,028,000	1,331	302,071,000
Research centers:						
Spec./comp. centers.....	53	54,609,000	54	57,865,000	54	57,865,000
Other Research:						
Research career programs.....	277	29,999,000	281	31,315,000	275	31,315,000
Cooperative clinical research.....	20	7,016,000	22	7,941,000	22	7,941,000
Other research related.....	60	21,095,000	61	22,141,000	61	22,141,000
Subtotal, other research.....	357	58,110,000	364	61,397,000	358	61,397,000
Total, research grants.....	1,650	388,119,000	1,717	411,290,000	1,743	421,333,000

Training:						
Individual awards:						
Noncompeting.....	144	2,522,000	144	2,595,000	142	2,595,000
Competing.....	116	1,954,000	116	2,011,000	114	2,011,000
Subtotal, individual.....	260	4,476,000	260	4,606,000	256	4,606,000
Institutional awards:						
Noncompeting.....	765	17,472,000	765	17,979,000	752	17,979,000
Competing.....	193	5,019,000	193	5,164,000	190	5,164,000
Subtotal, institutional.....	958	22,491,000	958	23,143,000	942	23,143,000
Total, training.....	1,218	26,967,000	1,218	27,749,000	1,198	27,749,000
Research & development contracts..						
(SBIR/STTR).....	31	11,643,000	34	12,981,000	32	12,509,000
	(1)	(375,000)	(1)	(387,000)	0	0
	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>	
Intramural research program.....	567	83,210,000	532	87,384,000	532	87,384,000
Research management and support..	299	30,631,000	315	28,333,000	315	29,174,000
Extramural construction.....	---	---	---	---	---	---
Total, NIMH.....	866	540,570,000	847	567,737,000	847	578,149,000
(Clinical Trials).....		(50,828,000)		(53,755,000)		(54,683,000)

Note: Includes FTEs associated with HIV/AIDS Research Activities. Funds to support these activities are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Extramural research and training.....	---	\$369,484	---	\$385,530	---	\$426,729	---	\$452,020	---	\$461,591	+	\$9,571
Intramural research.....	680	84,543	590	86,993	567	83,210	532	87,384	532	87,384	0	0
Research management and support.....	349	30,118	358	31,895	299	30,604	315	28,333	315	29,174	0	+841
Subtotal, obligations.....	1,029	484,145	948	504,418	866	540,543	847	567,737	847	578,149	0	+10,412
Unobligated balance, lapsing.....	---	199	---	291	---	27	---	---	---	---	---	---
Total, budget authority.....	1,029	484,344	948	504,709	866	540,570	847	567,737	847	578,149	0	+ \$10,412

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health
Summary of Changes

1996 Estimated budget authority.....	\$ 567,737,000
1997 Estimated budget authority.....	578,149,000
Net Change.....	+ 10,412,000

Changes:	1996 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
A. Built-in:				
1. Intramural:				
a. Within grade increase.....		\$36,867,000		+ \$526,000
b. Annualization of January 1996 locality pay raise.....		36,867,000		+ 234,000
c. January 1997 pay increases.....		36,867,000		+ 830,000
d. FECF, Unemployment compensation.....		36,867,000		+ 6,000
e. Service and supply fund increase.....		10,256,000		+ 297,000
f. Payment for centrally funded services.....		27,727,000		+ 2,376,000
g. Increased cost of laboratory materials and supplies.....		12,534,000		+ 276,000
Subtotal.....				+ 4,545,000
2. Research Management & Support:				
a. Within grade increase.....		19,808,000		+ 350,000
b. Annualization of January 1996 locality pay raise.....		19,808,000		+ 126,000
c. January 1997 pay increases.....		19,808,000		+ 446,000
d. FECF, Unemployment compensation.....		19,808,000		+ 5,000
e. Service and supply fund increase.....		3,278,000		+ 97,000
f. Payment for centrally funded services.....		1,241,000		+ 68,000
g. Increased cost of laboratory materials and supplies.....		4,006,000		+ 88,000
h. Relocation expense.....		7,284,000		+ 732,000
Subtotal.....				+ 1,912,000

Summary of Changes--continued

	1996 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting.....	880	215,123,000	-47	-5,912,000
b. Competing.....	364	68,079,000	+62	+13,284,000
c. SBIR/STTR.....	55	8,826,000	+17	+2,671,000
Total, research projects.....	1,299	292,028,000	+32	+10,043,000
2. Other research.....	364		-6	
3. Research training.....	1,218		-20	
4. Research and development contracts.....	34	12,981,000	-2	-472,000
5. Intramural research program.....		87,384,000		-4,545,000
6. Research management & support....		28,333,000		-1,071,000
Subtotal.....				+3,955,000
Total changes.....				+10,412,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Authority By Object

	<u>1996 Appropriation</u>	<u>1997 Estimate</u>	<u>Change</u>
Total compensable work years:			
Full-time equivalent employment.....	847	847	--
Full-time equivalent of overtime and holiday hours.....	5	5	--
Average ES salary.....	\$109,778	\$113,094	+\$3,316
Average GM/GS grade.....	10.1	10.1	---
Average GM/GS salary.....	\$45,550	\$46,917	+\$1,367
Average salary, grades established by PHS Act of 1955 (42 USC 207).....	\$55,105	\$56,758	+\$1,653
Average salary of ungraded positions.....	\$47,281	\$48,345	+\$1,064
Personnel compensation:			
Full-time permanent.....	\$30,517,000	\$30,353,000	-164,000
Other than full-time permanent.....	8,921,000	8,910,000	-11,000
Other personnel compensation.....	1,600,000	1,596,000	-4,000
Special personnel service payments.....	5,461,000	5,459,000	-2,000
Subtotal, personnel compensation.....	46,499,000	46,318,000	-181,000
Personnel benefits.....	9,963,000	9,918,000	-45,000
Benefits for former personnel.....	213,000	210,000	-3,000
Travel and transportation of persons.....	817,000	825,000	+8,000
Transportation of things.....	145,000	147,000	+2,000

	1996 Appropriation	1997 Estimate	Change
Rental payments to others.....	871,000	887,000	+16,000
Communications, utilities, and miscellaneous charges.....	1,802,000	1,824,000	+22,000
Printing and reproduction.....	892,000	930,000	+38,000
Other services:			
Consulting services.....	445,000	449,000	+4,000
Other services.....	6,009,000	6,069,000	+60,000
Purchases from government accounts.....	42,698,000	43,474,000	+776,000
Operation & maintenance of facilities.....	3,000	3,000	---
Research & development contracts.....	8,105,000	7,810,000	-295,000
Medical Care.....	710,000	711,000	+1,000
Operation & maintenance of equipment...	1,195,000	1,190,000	-5,000
Supplies and materials.....	5,260,000	5,225,000	-35,000
Equipment.....	2,892,000	2,895,000	+3,000
Grants, subsidies, & contributions.....	439,039,000	449,082,000	+10,043,000
Insurance claims and indemnities.....	177,000	180,000	+3,000
Interest and dividends.....	2,000	2,000	---
Total, budget authority by object.....	567,737,000	578,149,000	+10,412,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health
Administrative Costs

	1996 Estimate	1997 Estimate	Change
Personnel Compensation:			
Full-time Permanent (11.1).....	\$30,517,000	\$30,353,000	-164,000
Other than Full-time Permanent (11.3).....	8,921,000	8,910,000	-11,000
Other Personnel Compensation (11.5).....	1,600,000	1,596,000	-4,000
Special Personnel Service Payments (11.8).....	5,461,000	5,459,000	-2,000
Total Personnel Compensation (11.9).....	46,499,000	46,318,000	-181,000
Civilian Personnel Benefits (12.1).....	9,963,000	9,918,000	-45,000
Benefits to Former Personnel (13.0).....	213,000	210,000	-3,000
Travel (21.0).....	817,000	825,000	+8,000
Transportation of Things (22.0).....	145,000	147,000	+2,000
Rental Payments to Others (23.2).....	871,000	887,000	+16,000
Communications, Utilities, and Miscellaneous Charges (23.3).....	1,802,000	1,824,000	+22,000
Printing and Reproduction (24.0).....	892,000	930,000	+38,000
Consulting Services (25.1).....	445,000	449,000	+4,000
Other Services (25.2).....	6,009,000	6,069,000	+60,000
Purchases from Government Accounts (25.3).....	37,822,000	38,775,000	+953,000
Operations & Maintenance of Facilities (25.4)....	3,000	3,000	---
Research & Development Contracts (25.5).....	---	---	---
Medical care (25.6).....	710,000	711,000	+1,000
Operation & maintenance of equipment (25.7)....	1,195,000	1,190,000	-5,000
Supplies and Materials (26.0).....	5,260,000	5,225,000	-35,000
Total.....	112,646,000	113,481,000	+835,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

SIGNIFICANT ITEMS IN THE HOUSE
APPROPRIATIONS COMMITTEE REPORT1996 House Appropriations Committee ReportItem

Prevention Research - ... The House in its report 104-209, page 75, stated..."In keeping with the Committee's interest in NIMH support for prevention research, the Committee commends NIMH for developing an implementation plan to address the recommendations of the 1994 Institute of Medicine report "Reducing Risk of Mental Disorders: Frontiers for Preventive Intervention Research," and urges timely implementation of two areas of primary importance. First, to meet the need to train mental disorder prevention researchers, the Committee encourages NIMH to maintain its support for the B-START program, both for those at the beginning stages of their career and for career transitions to behavioral science research. Second, the Committee urges NIMH to take the lead among Federal research agencies in coordinating research efforts to prevent mental disorders."

Action Taken or to be Taken

A critical mass of prevention scientists, working in multidisciplinary environments of excellence, is needed to successfully develop the field. These researchers can then attract and mentor junior investigators. Consistent with the recommendations in both the IOM Report and the NIMH National Plan, the institute intends to encourage junior and senior researchers through mentored awards to "jump start" the field, increased use of minority supplements, and use of small grant mechanisms such as the B/START, Dissertation Research Grants, Fellowship awards, and Exploratory/ Developmental Grants.

The Institute plans to continue to exert leadership in research to prevent mental disorders through increased communication among interested agencies. NIMH already participates with other Federal components interested in early childhood research, including the Administration on Children, Youth and Families and the Department of Education. Building on these contacts and expanding them to include other components of government and areas of research can help lay the groundwork for potential research collaborations in the future.

Item

Autism - ...The House in its report 104-209, page 76, stated..."Last year the Committee encouraged NIH to implement a nationwide epidemiological study to determine the incidence of autism in the U.S. NIMH is funding the UNOCCAP Project, a large-scale investigation of the prevalence of various disease and disorder symptoms in children. The Committee encourages NIMH to collaborate with NICHD and include the symptoms of autism in its nationwide screening and follow-up efforts."

Action Taken or to be Taken

Last Spring NIMH, in collaboration with NICHD, NIDCD and NINDS, brought together a working group of distinguished scientists in the autism field to identify gaps in knowledge and to make recommendations for future research. A report will be published and NIMH will attempt to disseminate and implement the recommendations made by participants. Further, the NIMH Multi-Site Study of Mental Health Service Use, Needs, Outcomes, and Costs in Child and Adolescent Populations (UNOCCAP), will provide the nation's first estimates of the prevalence of developmental, mental, and emotional disorders in children, ages 4-17. Efforts are being made to include questions concerning autism and autism-spectrum conditions in the screening instruments of this large scale investigation.

Item

Violence - ...The House in its report 104-209, page 76 stated... "NIMH is encouraged to support research pertaining to behavior modification and attitude change within the general population and their role in increasing criminality and violence. This would also include the research questions involved in psychological profiling of violent, criminal, and destructive personalities."

Action Taken or to be Taken

In keeping with this recommendation, NIMH has begun a series of discussions with key researchers and Congressional staff focused on the ways in which groups influence violent behavior. NIMH is presently conducting a review of the research regarding cults, psychological processes, and violence. It is expected to contribute to our assessment of the research potential in these areas and will be part of discussion with NIH and other governmental agencies.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Authorizing Legislation

	<u>PHS Act/ Other Citation</u>	<u>U.S. Code Citation</u>	<u>1995 Amount Authorized</u>	<u>1996 Estimate</u>	<u>1997 Amount Authorized</u>	<u>1997 Budget Request</u>
Research and Investigation...	Section 301	42§241	Indefinite		Indefinite	
			Such sums as necessary	\$539,988,000	Such sums as necessary	\$550,400,000
National Institute of Mental Health...	Title IV, Part C	42§285				
National Research Service Awards.....	Section 487(D)	42§288	Such sums as necessary	27,749,000	Authorization Pending	27,749,000
Total, Budget Authority.....				\$567,737,000		\$578,149,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u>	<u>1/</u>
1993	n/a	n/a	\$574,803,000	\$583,651,000	2/
1994	\$576,015,000	\$613,444,000	613,444,000	613,444,000	
1995 3/	545,223,000	541,687,000	543,687,000	542,989,000	4/
Rescission				- 789,000	
1996	558,580,000 3/	661,328,000	550,632,000 3/	661,328,000	
1997 3/	578,149,000				

n/a = Not applicable.

1/ Reflects enacted supplementals, rescissions, and reappropriations.

Prior to the FY 1993 Senate Allowance, NIMH was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of \$4,723,000, \$81,000, and \$1,981,000.

3/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.

4/ Excludes enacted administrative reduction of \$561,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actuals	1996 Estimate	1997 Estimate
Office of the Director.....	8	9	10
Office of Prevention.....	3	3	3
Office on Equal Employment Opportunity.....	1	1	1
Office of Rural Mental Health Research.....	4	4	4
Office for Special Populations.....	5	5	5
Office on AIDS.....	9	11	11
Office of Legislative Analysis and Coordination....	5	5	4
Office of Scientific Information.....	22	20	20
Office of Resource Management.....	71	73	73
Office of Science Policy and Program Planning.....	10	10	10
Division of Neuroscience and Behavioral Science...	31	31	31
Division of Clinical and Treatment Research.....	51	50	50
Division of Epidemiology and Services Research....	49	49	49
Division of Extramural Activities.....	44	44	44
Division of Intramural Research Programs.....	530	532	532
Total.....	843	847	847
<u>Average GM/GS Grade</u>			
1993.....	10.2		
1994.....	10.2		
1995.....	10.1		
1996.....	10.1		
1997.....	10.1		

Note: Includes FTEs associated with HIV/AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute of Mental Health

Program Administration
Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
ES-6.....	2	3	3
ES-5.....	2	2	2
ES-4.....	10	10	9
ES-3.....	2	2	2
ES-2.....	1	1	1
Subtotal.....	17	18	17
Total - ES Salary.....	1,829,000	1,976,000	1,922,598
GS/GM-15.....	54	54	54
GS/GM-14.....	84	84	84
GS/GM-13.....	72	71	71
GS-12.....	71	71	71
GS-11.....	88	88	88
GS-10.....	2	2	2
GS-9.....	71	70	70
GS-8.....	43	43	43
GS-7.....	131	132	132
GS-6.....	28	28	28
GS-5.....	10	10	10
GS-4.....	30	29	29
GS-3.....	8	6	6
GS-2.....	1	0	0
GS-1.....	2	0	0
Subtotal.....	695	688	688
Total - GS/GM Salary.....	30,669,791	31,338,507	32,278,662
Grades established by Act of July 1, 1944 (42 U.S.C 207):			
Assistant Surgeon General.....	1	1	1
Director Grade.....	24	24	24
Senior Grade.....	16	16	16
Full Grade.....	12	12	12
Subtotal.....	53	53	53
Ungraded.....	101	95	89
Total permanent positions.....	634	641	641
Total positions, end of year.....	873	865	865
Total full-time equivalent (FTE) employment, end of year.....	843	847	847
Average ES level.....	4.0	4.0	4.0
Average ES salary.....	107,588	109,778	113,094
Average GS/GM grade.....	10.1	10.1	10.1
Average GS/GM salary.....	44,129	45,550	46,917

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

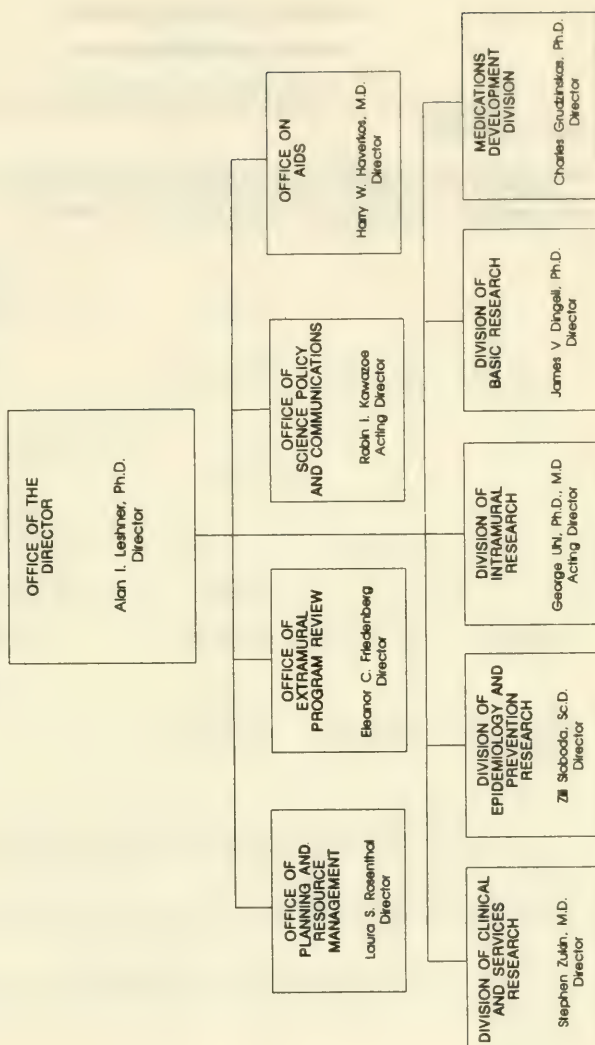
National Institute on Drug Abuse

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NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

For carrying out section 301 and title IV of the Public Health Service Act with respect to drug abuse, \$312,014,000.

Note—A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$290,280,000	\$458,441,000	\$312,014,000
Reduction in accordance with P.L. 103-333.....	-39,000		
Recission in accordance with P.L. 104-19.....	-212,000		
Subtotal, Adjusted Appropriation.....	290,029,000	458,441,000	312,014,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-248,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....		-153,331,000	
OD, NIH for Accounting Services.	-200,000		
Subtotal, adjusted budget authority.....	289,581,000	305,110,000	312,014,000
Unobligated balance, lapsing.....	-260,000		
Total obligations.....	289,321,000	305,110,000	312,014,000

1/ Excludes the following amounts for reimbursable activities carried out under this account : 1995 - \$2,678,000 ; 1996 - \$2,678,000; 1997 - \$2,800,000.

Also excludes funding for HIV activities: FY 1995 - \$147,347,000; FY 1997 - \$154,311,000 Included in the Office of AIDS Research, NIH.

Note: Excludes \$58,000 in FY 1995 and \$58,000 in FY 1996 for royalties.

JUSTIFICATION

NATIONAL INSTITUTE ON DRUG ABUSE

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
363	\$289,581,000	365	\$305,110,000	365	\$312,014,000	--	+\$6,904,000

INTRODUCTION

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute on Drug Abuse. Justification of NIH-wide FY 1997 activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The mission of the National Institute on Drug Abuse (NIDA) is to bring the power of science to bear on drug abuse and addiction. NIDA-supported research clearly demonstrates that drug abuse is a preventable behavior and addiction is a treatable disease -- a disease of the brain that is expressed in behavioral ways and in a social context. Last year NIDA celebrated its 20th anniversary. NIDA supported research is providing for these scientific and new approaches to make extraordinary progress in drug abuse research, building upon the scientific advances of the past two decades.

Among the most exciting discoveries is the molecular cloning of the receptor genes for virtually every major drug of abuse. NIDA has used this information to move beyond cloning to begin to understand the molecular and genetic bases of addiction. These discoveries have propelled us dramatically forward in cocaine research and we are now in a position to strategically develop effective pharmacological treatments for cocaine addiction. We have declared development of an anti-cocaine agent as NIDA's top priority. NIDA researchers in our intramural research program and NIDA-supported researchers in universities and other institutions across the country have also made exciting advances in their studies of opiate addiction. Several potential new therapeutic compounds have been identified, one has been approved by the FDA, and several other medications are under intense development for the treatment of opiate addiction.

The improvement and development of behavioral and psychosocial treatments are also essential in the battle against drug addiction and are necessary as adjunct therapies to ensure the success of pharmacologically based treatments. NIDA continues to assess the value of

integrating behavioral therapies with medications and to support studies to match specific types of patients to particular behavioral interventions.

While NIDA continues to focus most of its attention on cocaine and heroin addiction, NIDA continues to work on the problems of marijuana and its use, which has recently shown an alarming increase in use by young people. Last year, as part of a major Department of Health and Human Services initiative, NIDA launched a major prevention effort to reverse this trend. There is no doubt that marijuana is a behavioral toxicant. It changes the way people think, feel, and act, with consequences to the individual and to others, and does so long after the "high" disappears. Development of effective prevention and treatment strategies will incorporate the results of our basic research programs.

Another critical area in which NIDA continues to invest substantial research effort is the interplay between drug abuse and AIDS. The AIDS epidemic is now very closely tied to the drug epidemic and one cannot deal with either without the other. Drug abuse is currently the fastest growing vector for the spread of the human immunodeficiency virus (HIV), not only among drug users but also among non-drug using populations. According to data from the CDC, the majority of new HIV infections are associated with drug use. Most of these are injecting drug users (IDUs) who share infected needles, but an increasing number are crack addicts who are contracting the AIDS virus through unprotected sex.

The chronicity of the illness of drug addiction, the complex social and behavioral correlates, and the enormously devastating consequences make it imperative that NIDA continue its research efforts. Illegal drugs exact an enormous toll on the health of our Nation. That toll can be reduced by the development of more effective prevention and treatment strategies through research. Drug abuse prevention and treatment can work, and when they do, they significantly reduce drug use, improve social and psychological functioning, decrease related criminality and violence, and reduce the spread of AIDS.

STORIES OF DISCOVERY

Drug Abuse Outreach and Treatment Can Change HIV Risk Behaviors

Since AIDS was first identified in 1981, the disease has brought death and widespread physical and social devastation to people and nations worldwide. An estimated 1 million Americans today are infected with HIV, the human immunodeficiency virus, which causes AIDS; as many as 17 million people are infected worldwide. According to the Centers for Disease Control and Prevention (CDC), 470,288 cases of full-blown AIDS were reported in this country through the end of June 1995. Of these, approximately 60 percent have died. The critical connection between drugs and AIDS has become increasingly evident. As of June 1995, approximately 37 percent of all AIDS cases reported to the CDC were associated with injection drug use (IDU). Additionally, data from the CDC suggest that the majority of new HIV infections are associated with drug use. Groups at extremely high risk of infection include injecting drug users who share needles and other drug-use paraphernalia as well as

crack addicts who engage in unprotected sex with multiple partners. Also at high risk are sexual partners and offspring of these drug abusers.

NIDA's years of experience in developing and implementing drug abuse treatment and outreach programs have enabled the Institute to identify, study, and modify drug-use behaviors that increase HIV transmission risks among people who are in- and out-of-treatment. Importantly, and for some counter-intuitively, NIDA-supported studies have shown repeatedly that people still using drugs intravenously are nonetheless amenable to behavior change strategies. A study conducted in New York City demonstrated that multi-faceted risk reduction programs can produce large and significant and sustained decreases in HIV risk behavior among IDUs, even among those who continue their drug abuse. Among actively injecting addicts admitted for detoxification, the use of potentially contaminated syringes has declined from 51 percent of injections in 1984 to only 7 percent of injections in 1992. Further declines in unsafe injection practices were seen in addicts who participated in syringe exchange programs.

Additional NIDA-supported studies have reinforced these findings. University of Pennsylvania researchers studying heroin addicts in Philadelphia found that out-of-treatment subjects were injecting drugs, sharing needles, visiting shooting galleries, and practicing unsafe sex at significantly higher rates than in-treatment subjects. The study found that the addicts who did not receive treatment had a conversion rate to HIV-positive status that was six times higher than the rate among in-treatment injecting drug users who had been regularly exposed to risk-reduction education, counseling, and other strategies. Although drug treatment remains the preeminent means of reducing HIV risk among drug abusers, it has now been shown that much can be accomplished with addicts not yet able or willing to enter treatment. In San Francisco, a city where over half of all IDUs sampled in recent street settings participated in a syringe exchange program, the mean number of injections dropped from 1.9 to 0.7 per day during a six year period. The mean age of drug injectors increased by six years over this period and there was a decrease in the percentage of new injectors from 3 percent to 1 percent.

As the AIDS epidemic is becoming ever more closely tied to the drug epidemic, NIDA research has shown that behavior change is possible to save lives and other costs to society.

Progress in Understanding the Brain through Drug Abuse Research

At the time of NIDA's establishment, twenty years ago, there were major concerns about heroin and opiate addiction. As a result, NIDA-supported researchers began aggressively studying the neurobiological mechanisms for drug abuse. These studies rapidly led to the development of an animal model of drug self-administration and the discovery that animals will self-administer most drugs that people do. This model, as well as research on the brain-stimulation reward system, moved drug abuse research into the neuroscience laboratory. This move, coupled with the need to better understand and treat opiate addiction, sparked the search for the brain's opioid receptors and their endogenous ligands. With the landmark discoveries of endogenous opiate receptors by NIDA-funded researchers and the subsequent

isolation and characterization of endogenous opiates, the fields of neuroscience and drug abuse research became inextricably linked.

As drug abuse/neuroscience research continued to elucidate the sites and mechanisms of action of drugs of abuse, our understanding of the function and structure of the brain was propelled dramatically forward. In subsequent years, neuroscience researchers identified multiple receptors for opiates, as well as receptors for nicotine, cocaine, THC, the major active component of marijuana, LSD, and amphetamines. In the last few years, as part of NIDA's marijuana research endeavors, NIDA-funded investigators have identified the anandamides, the endogenous substances in the body that bind to the THC receptor. This discovery has opened up an entirely new avenue of research into the physiological role of these endogenous compounds and is leading to a better understanding of the consequences of marijuana abuse. Molecular neurobiology has also contributed heavily to drug abuse research. We have now identified and cloned the genes for virtually every drug of abuse. This achievement sets the stage for using rational drug design to develop new addiction medications. It also provides critical tools in the revolution that neuroimaging technology is bringing to drug abuse research. For the first time drug abuse researchers are able to actually visualize in real time where drugs like cocaine are binding in the brain, areas of the brain involved when an addict experiences "craving" and "withdrawal" and the sites of long term changes in the brain that result from chronic drug use.

It is clear that not only has neuroscience research revolutionized our thinking about drug abuse and addiction, but over the past twenty years drug abuse research has significantly impacted the evolution of contemporary neuroscience research.

Progress Towards Smoking Cessation and the Development of Nicotine Replacement Systems

Tobacco use, through cigarettes and smokeless tobacco, is the main avoidable cause of premature death in the United States. Each year, more than 400,000 Americans die from smoking related causes such as cardiovascular diseases, neoplasms, respiratory diseases, lung cancer, heart disease, and chronic airway obstructions. Most recently, smoking prevalence has stabilized among adults at about 26-27%. Prevalence of smoking among youth has increased over the last few years. In a NIDA-funded study, the University of Michigan reported that 33% more eighth graders smoked during the past 30 days in 1995 than was the case in 1991. These trends are similar for both males and females. Today, over 45 million Americans still smoke cigarettes. There are numerous economic and societal costs of smoking, including direct health costs and cost in years of life lost and increased illness suffered by smokers and also by non-smokers who suffer from involuntary smoke exposure. The estimated costs of medical, illness, deaths, and special conditions due to smoking were 72 billion dollars in 1990. Recent estimates of cigarette smoking by the Centers for Disease Control and Prevention found that, in 1990, cigarette smoking resulted in over 1 million years of potential life lost before age 65 and over 5 million years decrease in life expectancy.

During the past 25 years, research has demonstrated that nicotine, the main reinforcing agent in tobacco delivery systems, is an addictive substance which acts on the peripheral

nervous system, stimulating the ganglia, the central nervous system, the cardiovascular system, the gastrointestinal tract, and the exocrine glands. Nicotine is readily absorbed by numerous sites in or on the body and exhibits both stimulant and depressive phases of action. Withdrawal and craving symptoms often occur upon cessation of smoking. Treatment of nicotine addiction has had mixed results, despite the fact that most smokers report a desire to quit. Two forms of nicotine replacement systems, nicotine gum and the transdermal patch, are available to the U.S. market which act to produce gradual and better tolerated withdrawal.

The 1970s saw the coalescence of a directed research effort on nicotine addiction. As early as 1973, researchers investigated nicotine replacement systems, such as nicotine gum, in an effort to find therapies to aid in smoking cessation. In 1980, based largely on NIDA research, diagnostic criteria for tobacco dependence and withdrawal were included in the Diagnostic and Statistical Manual (DSM III) of the American Psychiatric Association. The research focus deepened in the 1980s and by 1983, NIDA supported researchers had created the prototype of the nicotine transdermal patch as well as demonstrated that nicotine met the criteria for a drug of abuse. The FDA approval of nicotine gum in 1984 marked the availability (by prescription) of the first nicotine replacement therapy on the U.S. market. Unfortunately, nicotine gum often has side effects such as nausea and jaw irritation, and many smokers are reluctant to use it and physicians reluctant to prescribe it. Dissatisfaction with nicotine gum prompted increased research into other areas of nicotine replacement therapy as well as a recognition that treatment of nicotine addiction must be accompanied by behavioral adjuncts, such as developing self-monitoring and coping skills. In 1991, the FDA approved the transdermal nicotine patch. The introduction of the patch was a major contribution in that it provides an improved nicotine replacement treatment in the U.S.

Since the introduction of nicotine gum and the transdermal patch, estimates based on Food and Drug Administration and pharmaceutical industry data indicate that more than 1 million individuals have been successfully treated for nicotine addiction. Building on this success, the testing of two additional forms of nicotine replacement systems, nicotine inhalers and nasal sprays, is now underway as potential treatments for additional smokers.

Progress in Developing Medications for the Treatment of Opiate Addiction

Addiction to opiates, such as heroin or morphine, exacts a heavy toll on our Nation. Opiate addiction is responsible for almost 15,000 deaths per year, costing society \$10 billion in lost productivity. A majority of these deaths are from HIV and hepatitis infection, which are spread mainly from needle sharing. About 50,000 opiate-related overdoses are reported by hospital emergency rooms each year. Direct medical expenditures for the health consequences of opiate dependence are about \$4 billion annually.

NIDA-funded research has been pivotal in determining the neurobiological basis of opiate addiction and in the development of effective treatments. Research initiated in the 1970s was aimed at understanding the sites in the brain where opiates have their action and the mechanism by which addiction occurs. This early research, with the discovery of the opiate receptors and the endogenous opiates, elucidated not only the site of action of opiates but revolutionized our thinking about the role these compounds play in the body.

Research conducted during the 1960s identified methadone as a potentially effective medication for the treatment of heroin or other opiate dependence. Subsequent research identified therapeutic doses of methadone that, when taken orally, do not produce heroin's rush and last 24 hours in the system. This research has identified effective dosage levels and found that the effectiveness of methadone maintenance for many is significantly improved by concurrent delivery of rehabilitative and other clinical services.

Since the early 1970s NIDA has supported a considerable amount of research to improve methadone treatment and to develop additional medications for opiate addiction, LAAM, naltrexone, and buprenorphine. LAAM is similar to methadone, but stays in the system longer. Daily, oral administration of methadone or alternate-day or twice weekly administration of LAAM reduces the need for opiate dependent individuals to inject drugs. By decreasing injection drug use, treatment helps reduce the spread of diseases that are transmitted through needle/syringe sharing, including HIV infection. In addition, studies have shown that untreated addicts have an 8-14 fold higher death rate than matched controls, and a 7-8 fold higher death rate than patients on methadone maintenance therapy. This is probably a reflection of the adverse events that are associated with injection drug use and the addict lifestyle, such as overdose, accidental death, medical complications, and high rates of violence.

In the last few years molecular neurobiology has made possible the cloning of the genes for a number of different opiate receptors in the brain. This achievement provides valuable data to strategically develop new anti-opiate medications by providing detailed information on the targets to which these medications must bind. Most recently, NIDA-funded opiate research has discovered a new opiate-like brain peptide that may function as a neurotransmitter. This explosion of new discoveries will not only open new avenues for understanding and treating addiction but will bring dramatic insights into the physiological and biochemical mechanism of action of opiates in other parts of the body such as the spinal cord, gastrointestinal tract and immune system.

ANNUAL SCIENCE ADVANCES

Prenatal Cocaine Adversely Alters Brain Structure: Daily cocaine administration has been found to cause abnormalities in fetal brain development. Researchers have demonstrated that daily cocaine administration to pregnant non-human primates in doses comparable to those found in human abusers led to severe abnormalities in the migration of neurons (a critical process in brain development), the number of neurons present after birth, and the structure of supporting cells in the cerebral cortex. When postnatal brains were examined, severe disruptions of the normal structure of the cerebral cortex were found and the number of neurons and nonneuronal cells was found to be decreased by 10-15% in certain layers of the cerebral cortex. This is the first study to demonstrate clearly defined structural changes in the cerebral cortex. Findings such as these have implications for understanding behavioral and learning difficulties in children exposed prenatally to cocaine. (M.S. Lidow, 1996. Prenatal Cocaine Exposure Adversely Affects Development of the Primate Cerebral Cortex. Synapse, In Press.)

New Opiate-Like Brain Substance Discovered: Researchers have discovered a new neuropeptide (orphanin FQ) in the brain which may represent a whole new class of neurotransmitters. Although orphanin FQ and its receptor are similar to opioid peptides and their receptors, surprisingly, orphanin FQ produced increased sensitivity to pain rather than the expected analgesic effect. This discovery opens a new line of research and begins to elucidate receptor systems extending beyond those for the classical opiate drugs. It may have major implications for understanding the mechanisms underlying addiction as well as for advancing our ability to treat pain. (*Science* Vol 270:792-794.)

Long Term Negative Consequences of Prenatal Exposure to Phenobarbital: Prenatal exposure to phenobarbital, a barbiturate, has been found to have measurable effects that extended into adulthood. Researchers studied 114 men born between 1959 and 1961 in Copenhagen, Denmark, who were exposed prenatally to phenobarbital. With other variables matched and statistically controlled, the results of intelligence tests showed that the group exposed to phenobarbital had significantly lower scores than those not exposed to the drug. This study advances our understanding about the profound effects of parental drug use on the health and development of children. Phenobarbital is a legally prescribed drug that also has abuse potential. Researchers concluded that physicians should use increased caution in prescribing barbiturates during pregnancy. (Machover Reinisch, *JAMA*, Vol. 274, No. 19, Nov 15, 1995.)

Rats Have Been Successfully Immunized Against the Psychostimulant Effects of Cocaine: NIDA funded researchers have successfully immunized rats against the psychostimulant effects of cocaine and opened up the possibility of developing a vaccination against cocaine addiction. Rats were immunized with an antigen that causes the production of antibodies to cocaine. When these rats were then given cocaine, there was a dramatic reduction in behaviors associated with the psychostimulant effects of cocaine when compared to control animals that were not immunized. In addition, brain areas where cocaine mediates its effects had substantially lower concentrations of cocaine than the same areas in nonimmunized animals. These results are an exciting breakthrough in NIDA's efforts to develop a medication for the treatment of cocaine addiction and they offer the scientific and medical fields a promising new direction in the search for a safe means of blocking the damaging effects of crack and cocaine. (Rocio et al., *Nature* December 14, 1995.)

School-based Prevention Program Reduces Teen's Drug Use Through the End of High School: A long-term study shows that drug abuse prevention programs, when conducted with seventh grade students and reinforced with subsequent "booster" sessions, can produce lower levels of tobacco, alcohol, and marijuana use by teenagers over a sustained period of time. Positive effects of this intervention remained with a majority of students. The Life Skills Training Program combined training in the skills and knowledge to resist social pressure to use drugs and in basic interpersonal skills with information about the risks and prevalence of drug abuse. Researchers concluded that an effective school-based drug abuse prevention program for young teenagers must address a wide range of interpersonal skills, relationships, managing anxiety, and resisting social pressure. Such a program must also begin in junior high school and include at least 2 years of booster sessions to be effective. (G. J. Botvin, *JAMA*, Vol 273, No. 14, April 12, 1995.)

MDMA (Ecstasy) Causes Permanent Changes in the Brain: MDMA ("Ecstasy"), a synthetic drug with hallucinogenic and amphetamine-like properties, has been found in numerous studies to cause degeneration of nerve axons and terminals that contain the neurotransmitter serotonin. This NIDA funded study demonstrates for the first time that, although the nerve terminals and axons will regrow, they do not grow back normally. After regrowth, some brain areas that are normally contacted by these axons do not receive connections and other areas that do not normally receive connections now do. These abnormal reconnections may lead to permanent changes in the brain that could result in cognitive impairments, changes in emotion, learning, memory, or neuroendocrine abnormalities. Abnormal changes similar to those seen with MDMA may also occur in certain neurodegenerative diseases, such as Alzheimer's or Parkinson's disease, suggesting the importance of determining the mechanism for the abnormal reconnections. (C. Fischer, 1995. *The Journal of Neuroscience*, 15(8):5476-5485.)

Marijuana Can Produce Addiction: A recent NIDA study has shown that tetrahydrocannabinol (THC), the active ingredient in marijuana, can produce addiction. Addiction can be experimentally demonstrated when a drug is either abruptly withdrawn or a blocker is administered. In this study, rats were treated with THC for several days and then given a THC blocker to precipitate withdrawal. After the administration of a THC blocker, rats displayed pronounced withdrawal symptoms typical of those seen with withdrawal from other drugs, indicating addiction to THC. The availability of a functional experimental model for cannabis dependence allows for the systematic study of the consequences of chronic exposure to cannabinoids and for the development of treatment strategies for individuals who become compulsive cannabis users. (B. Martin, 1995. *European Journal of Pharmacology*, Vol. 282, R2-2.)

Endogenous Opioids may be Involved in Nicotine Dependence: Smokers' ability to quit is compromised by the nicotine abstinence syndrome. Using a rat model of the nicotine abstinence syndrome, it has been demonstrated that nicotine withdrawal signs are similar to those of moderate opiate abstinence. Furthermore, these signs can be precipitated not only by a nicotine antagonist, but also by the opiate antagonist naloxone. In addition, in nicotine dependent rats, withdrawal signs were reversed by morphine as well as nicotine itself. These results support the hypothesis that the release of endogenous opioids plays a role in nicotine dependence. A greater understanding of the neurobiological mechanisms underlying nicotine addiction may lead to more effective treatments for people wishing to quit smoking. (David Malin, R01DA08260)

Cigarette Consumption and Cigarette Seeking Behavior can be Decreased by Increasing the Cost and Offering Alternative Activities: A NIDA-funded study has demonstrated that cigarette consumption and cigarette seeking behavior can be decreased by principles derived from behavioral economics. Cigarette smokers participated in a laboratory study in which work effort ("simulated employment") reduced cigarette consumption, as did the availability of recreational activities. The greatest reductions in both cigarette smoking and effort to obtain cigarettes were achieved when smoking cost was increased in combination with the presence of alternative recreational activities. This study points out yet again that both drug

seeking and consumption are not intractable and can be reduced by interventions informed by models in the basic behavioral sciences. (Bickel, Experimental and Clinical Psychopharmacology, 3, 1995.)

Opiate Receptors May Play a Role in Craving: A NIDA-funded study has shown that an increase in mu-opiate receptor binding in certain brain regions may be associated with craving. Mu-opiate receptor binding was compared between cocaine dependent and cocaine non-dependent men using the brain imaging technology, positron emission tomography (PET). Mu-opiate receptor binding was 25-50% higher in several brain regions in cocaine-dependent men as compared to non-cocaine users. Furthermore, craving was significantly correlated with the mu-opioid binding. These increases were still observed after four weeks of monitored cocaine abstinence in the majority of subjects. These findings demonstrate for the first time the involvement of the endogenous opioid system in cocaine dependence and cocaine craving in living human subjects (JK Zubieta et al., presentation at the 42nd Annual Meeting of the Society of Nuclear Medicine, June-12-15, 1995, Minneapolis, MN).

Comparison of Education vs. Behavioral Skills Training Interventions in Lowering Sexual HIV-Risk Behavior of Substance-Dependent Adolescents: Training based on cognitive-behavioral principles may be effective in lowering high-risk adolescents' vulnerability to HIV infection. Substance-dependent adolescents in a residential drug treatment facility received either a 6-session behavior skills training HIV-risk reduction intervention or standard HIV education. After the intervention, adolescents who received behavior skills training exhibited increased knowledge about HIV-AIDS, more favorable attitudes toward prevention and condom use, more internal locus of control, increased self-efficacy, increased recognition of HIV risk and decreases in high-risk sexual activity. Self-report data were corroborated by records for the treatment of sexually transmitted diseases. (JS St. Lawrence, Journal of Consulting and Clinical Psychology 63(1):154:157.)

Prevention Efforts Can Reduce the Spread of HIV Among IDUs: A NIDA funded project examined case histories of five cities in which HIV seroprevalence has remained low despite the introduction of HIV into a heterosexual IDU community. The case studies were conducted to identify common elements of prevention in the communities that could serve as models for other communities with similar HIV/IDU profiles. Three common prevention components were identified: 1) beginning early, 2) community outreach, and 3) access to sterile injection equipment. This study suggests that by implementing certain prevention efforts it is possible to severely limit transmission of HIV among populations of IDUs despite continuing risk behavior among a substantial proportion of the population. (D. Des Jarlais, JAMA, 274:1226-1231, 1995.)

Increased Smoking and Drug Use Among Students: Results of the 1995 Monitoring the Future Study (MTF), supported by a NIDA grant and the University of Michigan (L. Johnston, Principal Investigator) indicate that use of cigarettes, marijuana and other illicit drugs increased among students in all three grade levels surveyed. In addition, fewer students expressed negative perceptions of drug use. In most cases, these changes continued recent trends that began in the early 1990s and reversed a decade or more of decreases in drug use.

These results demonstrate the critical importance of education and prevention efforts for preventing young people from engaging in drug use.

Enhanced Outreach Efforts Decrease Risk Behaviors Associated with the Transmission of HIV: NIDA-funded studies show that six-months after exposure of IDUs and their sexual partners to interventions consisting of street-based outreach and risk reduction and pre- and post-test HIV antibody counseling, there are significant reductions in risk behaviors. There is a 41% decrease in the number of times individuals inject drugs, a 54% reduction in needle sharing, and a 36% reduction in having sex with an IDU. These studies demonstrate that it is possible to reduce risk behaviors associated with the spread of HIV even among active drug users.

Behavior Therapy Effective for Substance Abusers: Eighty-two adult and older adolescent subjects were enrolled in a study designed to assess the efficacy of a behavioral approach that included combined elements of urge control training, behavioral contracting, and imaginal rehearsal of consequences of drug use. Efficacy was assessed in a randomized comparison with a group discussions/peer support condition that focuses on the expression of thoughts and feelings associated with drug use. Results suggest that the behavioral condition is more effective in reducing drug use 12 months after entry into treatment, and more effective across gender, age, educational level, and type of drug use (e.g., opiate; cocaine; marijuana). Greater improvement was also noted in subjects enrolled in the behavioral intervention on measures of school/employment attendance, family relationships, and number of contacts with the police. (N.H. Azrin, *Behav. Res. Ther.* 32(8):857-866)

Heavy Use of Marijuana is Associated with Cognitive Impairment in College Students: Heavy marijuana users (median 29 days in the last 30) were compared with light marijuana users (median 1 day in the last 30) on several neuropsychological tests following at least 19 hours of abstinence. The tests included: general intellectual functioning, abstraction ability, sustained attention, verbal fluency, and ability to learn and recall new verbal and visuospatial information. Heavy users displayed significantly greater impairment than light users in several of these tests. These differences remained after controlling for potential confounding variables, such as estimated levels of premorbid cognitive functioning, and for use of alcohol and other substances in the two groups. Whether this cognitive impairment is due to a residue of drug in the brain, a withdrawal effect from the drug or a neurotoxic effect of the drug, is not clear. (H.G. Pope et al., *JAMA*, February 1996)

Buprenorphine and Buprenorphine Combined with Naloxone for the Treatment of Opiate Dependence: Clinical studies of buprenorphine (a partial opiate agonist) have demonstrated it to be safe and effective for treating heroin dependency and support a New Drug Application to the FDA. Buprenorphine will aid in the treatment of heroin addiction by substituting for heroin at opiate receptors and preventing withdrawal symptoms. Formulation and pharmacokinetics work is currently well under way for the development of a tablet containing buprenorphine and naloxone (an opiate antagonist). Clinical testing of the combination of buprenorphine and naloxone will begin in 1996. The addition of naloxone will help prevent the diversion and injection of buprenorphine.

BENEFITS AND IMPACT OF RESEARCH

Cost of drug abuse

When one considers the costs associated with drug abuse -- such as AIDS, crime and violence, drug-exposed babies, teen pregnancy -- and the millions of lives ruined by drug abuse and addiction, it is apparent that the investment in research is essential, reasonable, and justified and the best hope for continued gains the understanding of drugs of abuse, their consequences and correlates and in the development of knowledge-based drug abuse prevention and treatment approaches. Drug abuse research also represents an extremely wise and ultimately profitable investment, not only in terms of dollars, but also, and more importantly, in terms of the future of our Nation and the lives of our children and our children's children.

The total annual economic costs to society of drug abuse are estimated to be \$67 billion; the costs of nicotine addiction and smoking cigarettes add another \$72 billion [Rice, 1990]. Costs related to AIDS continue to dramatically increase each year, with injection drug users and their sexual partners comprising the fastest growing segment of the HIV population. Recent CDC findings show that, as of June 1995, approximately 3 in 8 cases of AIDS were related to injection drug use.

We can reduce this price tag by improving prevention and treatment through research. Several conservative estimates show that for every \$1 invested in addiction treatment programs, there is a return of between \$4 and \$7 in reduced drug-related crime, criminal justice costs, and theft alone. When savings related to health care are included, total savings can exceed costs by a ratio of 12 to 1. A study published in 1994 by the RAND Corporation demonstrated that drug treatment was 7-23 times more cost effective than criminal justice programs.

Pharmacotherapies

Substantial progress has already been made in the development of effective medications for treating drug addiction. Current pharmacotherapies like methadone and LAAM do work, and not only save lives but allow people to lead more productive lives. In the next decade research discoveries will permit the development of even more effective medications to treat the chronic, relapsing disease of drug addiction.

NIDA is now bringing together discoveries in molecular neurobiology, neurochemistry and neuropharmacology to systematically develop medications for the treatment of cocaine addiction. This revolution in neuroscience is providing the stimulus for dramatic changes in the way in which cocaine addiction is treated. NIDA research initiatives that focus on using new technologies, such as brain imaging techniques to visualize the process of addiction, are helping to move twenty years of basic research into the clinic.

Recent research advances in drug addiction have already paid off in enhanced treatments, and will result in even more effective treatments over the next decade, as our ability to

capitalize on these advances continues to expand. We have now identified and genetically specified the molecular sites in the brain where every major drug of abuse, including cocaine, has its initial effect. These discoveries, together with computer-aided drug design, should enable us to rationally develop, synthesize, and test novel compounds to break the cycle of drug addiction, based on our understanding of exactly how and where drugs of abuse work in the brain. We have identified endogenous opiate systems in the brain that are involved in drug addiction, pain, and other diseases and physiological functions. We have identified the brain receptors for the active ingredient of marijuana, delta 9 tetrahydrocannabinol, and have discovered endogenous brain chemicals that act on these receptors. Additionally, the development of naltrexone as an opiate blocker has directly benefited other fields and disciplines and is now showing promise in the treatment of alcoholism and sudden infant death syndrome and is routinely used in emergency room settings for treating comatose patients. We have also enhanced our abilities to treat drug exposed children, measure the extent of drug abuse in various populations, treat cocaine abuse using behavioral techniques, measure the abuse potential of new drugs, specify the neurotoxicological effects of drugs, and use methadone, LAAM, and other interventions to help prevent HIV.

Behavioral Therapies

Behavioral therapies, including a range of psychosocial interventions, are the most frequently administered treatments for drug addiction and remain the only available treatment approaches for many drugs of abuse. Behavioral interventions also serve as adjuncts to pharmacological treatments, addressing concomitant interpersonal and environmental problems and facilitating medications compliance.

While considerable progress has been made over the past decade in developing effective behavioral therapies, treatment retention and relapse remain problematic largely due to the fact that the provision of these services has not been standardized and many of the behavioral therapies administered for drug addiction have been adapted from established therapies which do not focus on treating drug addiction. In 1994, NIDA launched the Behavioral Therapies Development Program, which applies the same controlled evaluation process as is used in evaluating new medications to the assessment of behavioral therapies.

This Initiative is building on the knowledge gained from past and ongoing studies to identify promising therapies that will undergo a rigorous three-stage process that involves formulating, testing and refining the therapies in a series of small-scale studies, larger clinical trials, and replication studies in different treatment settings. Following this evaluation, NIDA will endorse particular therapies, support the development of manuals to provide systematized guidance on how to implement the particular therapy, and promote widespread application by treatment practitioners. Future research and evaluation efforts will examine the effects of the therapies over time, i.e., within the next 1-3 and 5-10 years, providing follow-back data to ensure that the therapies and manuals are updated as needed to reflect current treatment practices and patient needs. Practitioner and patient groups will be significantly involved in any research or evaluation effort to examine the long-term effectiveness of the therapies and manuals. Ultimately, NIDA plans to work collaboratively with the Center for Substance

Abuse Treatment (CSAT), SAMHSA, to disseminate proven therapies to counselors and therapists in community drug abuse treatment clinics.

The Changing Face of the AIDS Epidemic

AIDS is being transformed from being primarily a disease of gay white men who aggressively seek all avenues of health care to being primarily a disease of drug abusers and their families who seek care only later in the course of disease progression and with less success. The stimulus for this transformation is the success of educational and behavior change interventions in the gay community and the limited gains of such effective intervention targeted at drug abusers and the communities in which they live. Major research programs are needed to develop effective interventions and treatments that will significantly change the high-risk behaviors of drug abusers and addicts and address both the transmission of HIV and its clinical progression in drug abusers, their sex partners and their children. One such study funded by NIDA has recently demonstrated that it is possible to significantly reduce high risk for AIDS drug use and sexual behaviors among injecting drug users (IDUs). NIDA initiated the study, the National AIDS Demonstration Research Project, to educate out-of-treatment IDUs and their sex partners about HIV prevention mainly through community-based outreach interventions.

Major initiatives in clinical medicine and health services research are under way at NIDA related to effective treatment of HIV in drug abusers to address the issue of disease progression and access to care for HIV. Street-based epidemiology and ethnography research is being addressed to the issue of HIV transmission. These are providing essential baseline information against which to compare the effects of current and future interventions.

Facing the Future

With science now demonstrating that drug addiction is a disease of the brain expressed in behavioral ways and in a social context, it is increasingly clear that the problems of drug abuse and addiction require that we enlarge our horizons. The study of drug abuse and addiction is more than the study of drug receptors, more than the study of drugs as reinforcers, and more than the study of young people after they have gotten into trouble with drugs. To study drug abuse and addiction properly requires that we expand our research program and look at a broad range of factors that affect drug abuse and addiction. NIDA is now positioned as never before to meet those challenges through a rigorous, comprehensive program of research disciplines whose findings will guide the development of even more effective prevention and treatment programs.

INNOVATION IN MANAGEMENT AND ADMINISTRATION OF NIDA

Over the past year, NIDA has undertaken a number of activities to ensure the efficient utilization of its resources and their availability to support the research mission of the Institute. During this process, the Institute has sought the input of inhouse workgroups as well as from outside scientists, health professionals, and the lay public. A number of changes have been made during the year that have resulted in reduced administrative expenses and in the redirection and more focused utilization of resources to support research of the highest quality and priority. These have included changes in the means for providing administrative support, a reassessment of certain grant mechanisms used for supporting research conducted at universities, and collaborative administrative and research programs with other organizations, both government and private, that maximize the expertise available from all sources. The following discussion provides examples of some of these activities.

As part of the changing culture in government management, NIDA has undertaken sustained and indepth reviews of several aspects of its administrative and management programs and policies. This has resulted in a number of innovations in the internal administration of the Institute and in the management of its research portfolio. During this effort, NIDA has reorganized the structure of its extramural divisions, streamlined its paperflow and eliminated unnecessary levels of review, made arrangements to receive administrative services from other Institutes, or to provide services to them, and reviewed the effectiveness of several grant mechanisms for accomplishing particular research objectives. NIDA views the changing culture as an opportunity to take a fresh look at the efficiency and effectiveness of its processes and programs, and expects to build on the examples described below during the upcoming years.

Administrative Innovations. NIDA has been involved in several streamlining efforts designed to maintain its research capability and to ensure the quality of its scientific programs while accommodating to FTE reductions and reduced administrative resources. As part of the NIH streamlining effort, NIDA developed plans to help meet targeted reductions in FTE ceilings, control positions, and supervisory ratios through 1999. NIDA has already restructured the organization of its extramural program, resulting in a 22 percent reduction in the number of extramural branches and an associated decrease in supervisory positions. Perhaps more importantly, the reorganization has resulted in enhanced program effectiveness and has allowed the Institute to more easily address changing scientific priorities. By design, it has resulted in a more effective infusion of neuroscience throughout the Institute, broadened the base for behavioral science, built a stronger clinical etiology and treatment program, enhanced services research, and focused the Institute's epidemiological efforts. The structure of the Intramural Research Program will likewise be examined during the coming year to review the effectiveness of its organization for accomplishing its research objectives.

NIDA has also made several organization and systems changes to the ways in which it provides administrative support to its research programs. Arrangements have been established with other NIH Institutes for NIDA to receive certain administrative and research support services from them, as a means to reduce its administrative costs and to more effectively use its resources. As part of the NIH overall streamlining efforts, NIH developed and established

a new program for the Institutes to receive and provide services to each other, building upon the principles of economies of scale and focused expertise to improve efficiencies while ensuring quality services. NIDA is participating in five of these newly-established NIH Competitive Service Centers, the most of any NIH ICD. As part of this activity, the NIDA Intramural Research Program (IRP) is participating in a technology transfer service center being run by another Institute with substantial technical expertise in this area, and is receiving assistance in the negotiation of technology transfer agreements (such as CRADAs), to expand its abilities to conduct research collaboratively with academia and industry partners. Other parts of NIDA are participating in service centers being run by other Institutes providing administrative and research support services in the areas of personnel recruitment activities, technical support for the development and maintenance of the NIDA computer network and workstation support, grants management tracking of payback obligations for research trainees and fellows, and the acquisition of station support contracts and procurements. These arrangements with other NIH Institutes will allow NIDA to receive from them certain administrative support services which normally require inhouse administrative personnel to provide, thus allowing for both the receipt of high quality services and the redirection of resources to the research programs.

In addition to the use of competitive service centers, NIDA has established other types of collaborative arrangements with other NIH Institutes to share resources in order to achieve greater FTE efficiencies and cost reductions. For example, during the past year, the NIDA Intramural Research Program, located in Baltimore, has developed several arrangements with the Intramural Gerontology Research Center (GRC) of the National Institute on Aging, also located in Baltimore, including the sharing of veterinarian services and of library resources. Discussions are underway with GRC to expand these arrangements to areas such as use of the NIDA animal care contract, use of the NIDA PET facility and associated technical services, establishment of a joint safety program, and sharing warehouse storage space. The NIDA Intramural Program has also shared its lease and contract mechanisms with the National Center for Human Genome Research in order to assist them in the start-up of their new research center to be located in Baltimore. Such arrangements as these are beneficial to each of the Institutes involved and help facilitate the maximum deployment of resources for the conduct of research and support of the research scientists.

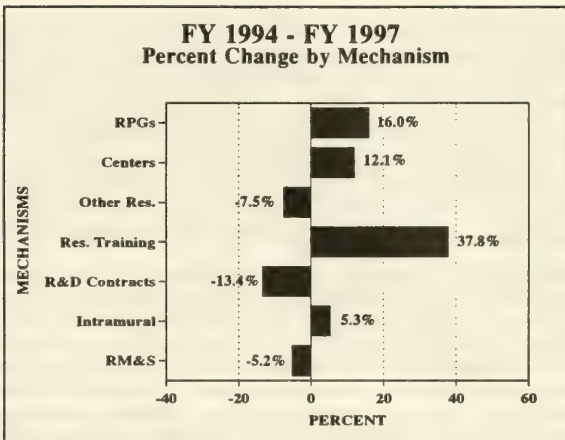
NIDA expects other opportunities for administrative change to occur over the next few years. For example, both the NIDA personnel management branch and the management analysis and services branch currently have significant responsibilities in different aspects of the human resources management area. In order to take advantage of the changes occurring government-wide and through NIH re-engineering activities in the human resources management area, NIDA is consolidating these branches. By doing so, services to NIDA programs will become more efficient and based on a wider base of expertise. Moreover, FTE reductions may also be achieved over the longer-term as a result of planned staff cross-training and sharing of support staff across the administrative areas.

Program Management Innovations. In addition to innovations in its systems of administrative management, NIDA has also undertaken reviews of the management of its research programs per se, to ensure that the current mechanisms of support are the most

particular research and program objectives. Over the past two years, NIDA has begun an assessment of the use of particular mechanisms for funding grant and contract programs. One result has been a decrease in the use of the research and development contracts mechanism. Although this mechanism is necessary and is the most effective vehicle for accomplishing certain program objectives, such as in the medications development program, other projects previously supported through the contracts mechanism could more effectively and appropriately be supported and performed as research grants. Reducing the funding through the contracts mechanism has also meant enhanced availability of funds for the competitive grant mechanisms. As can be seen from the chart below, since FY 1994, NIDA has increased funds for research project grants by 16%, and has reduced funding for contracts by over 13%.

A review was also conducted during the past year of the NIDA Research Centers program, to ensure that the maximum scientific and programmatic benefits were being gained by the use of this grant mechanism. As a result of this review, new types of center programs will now be supported by NIDA and policies were developed that clarify the role of center grants to serve as an enabling vehicle for the conduct of cutting edge research that would not or could not be conducted without the existence of the center. New guidelines published by NIDA emphasize the role of centers to foster inter- and multi-disciplinary collaborations and require center grant applications to demonstrate that the center has the potential to become a significant regional or national scientific resource. These new policies, together with revised criteria and procedures for the review of center applications, should help to ensure the effective use of these resources and the most effective match of this important funding mechanism with the accomplishment of particular scientific program objectives.

During the past decade, the rapid explosion in the research advances and opportunities, particularly in the neurosciences, has created a demand for a greater pool of well-trained drug addiction research scientists. Accordingly, NIDA has a compelling interest in attracting new scientists to the field of drug addiction research, and has placed an emphasis on the support of research training grants and fellowships. Moreover, because of the need to attract clinical researchers and provide advanced training in the newest techniques to current scientists, NIDA has also utilized several types of innovative research career awards. Since FY 1994, NIDA has increased funding support for research training by 38%, and this priority continues in the FY 1997 budget.



Public/Private Partnerships

NIDA has used public/private partnerships to leverage its resources and decrease the timeframe within which the objectives of a research project can be accomplished. This has been a particularly useful method in the medications development area, where the amount of time and resources necessary for preclinical and clinical testing of compounds to develop new treatment medications can be quite extensive. These collaborations through material transfer agreements and CRADAs often allow NIDA access to otherwise unobtainable proprietary compounds and critical supporting data. They also allow each party to concurrently focus on a different role in developing data necessary for product approval and subsequent marketing. For example, through CRADAs, NIDA often saves years of time and millions of dollars by not having to synthesize compounds, make human dosage forms and matching placebos, and not having to repeat pharmacokinetic and toxicological testing which may already have been performed by a private sector entity. Such arrangements not only save resources, but they hasten the process for the development of more effective medications and treatments for drug addictions. Consistent with the overall NIDA priority, the emphasis in this area is now on partnerships to facilitate the development of a medication for the treatment of cocaine addiction.

Trans-NIH Collaborations

NIDA seeks to make the most effective use of its own resources by taking maximum advantage of expertise and resources available outside of the Institute. NIDA therefore collaborates with several NIH institutes and other Federal agencies on a wide range of research projects, both intramurally and extramurally. These arrangements enable the

organizations to combine their scientific expertise to study areas beyond what they could do individually. Since each agency focuses on their specific area of expertise, broad goals of the project can be met. Within the NIH, NIDA utilizes various mechanisms for these collaborative arrangements, including the joint funding or conduct of specific research projects, the joint sponsorship of grant Program Announcements, collaborative workshops or conferences, and the provision of scientific advice and assistance.

For example, NIDA supported research has both contributed to and benefitted from the wide range of neurosciences research supported at the NIH. As such, NIDA research is a key component in the NIH investment area of the biology of brain disorders. This initiative will be a broadly-based effort among several NIH institutes to understand the biology of the mammalian brain and to apply that knowledge to the diagnosis, prevention, and treatment of disease. Areas of particular promise that will involve NIDA include molecular genetics, neuronal signalling, and behavior of complex brain system disease. NIDA is also a collaborative partner in the Human Brain Project, a consortium of several NIH institutes, the National Science Foundation, the Office of Naval Research, and the National Aeronautics and Space Administration, which has as its goal the development of a computer network of neuroscience information available to researchers throughout the world. NIDA continues to be a major participant in this joint project.

NIDA also participates in a wide range of trans-NIH collaborative efforts, ranging from behavioral studies on nicotine dependence with the National Cancer Institute, to studies of the impact of HIV infection in women with the National Institute of Allergy and Infectious Diseases, to investigation of the acute and long-range effects of prenatal drug exposure on infants, with the National Institute of Child Health and Human Development.

(In addition to research and programmatic collaborations, NIDA is also involved in numerous trans-NIH collaborations in the administrative area, several of which were discussed earlier.)

FY 1997 BUDGET OVERVIEW

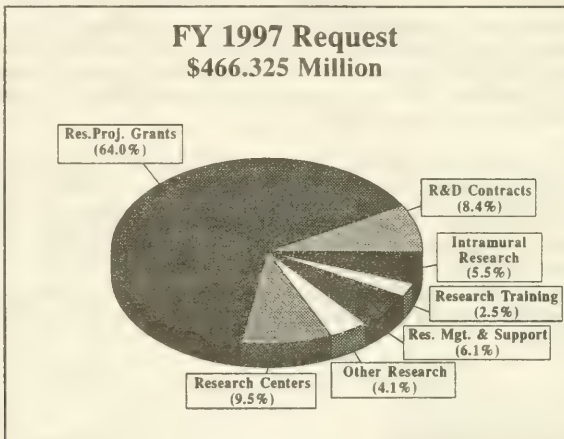
The FY 1997 Estimate for NIDA totals \$312,014,000, and reflects an increase of \$6,904,000, or 2.3%, over the comparable FY 1996 level of \$305,110,000.

In the FY 1997 President's Budget Request, NIDA support for research project grants (RPGs) would increase by 2 percent over FY 1996. NIH proposes to revise increases identified in the Cost Management Plan to parallel program budget increases of 1.64 percent over the FY 1996 level requested in the FY 1997 President's Budget. For FY 1997, inflation is projected at 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997 noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent over FY 1996. These levels will maintain stability of support within the extramural grantee community while

providing new research opportunities by supporting 218 competing RPGs, an increase of 22 competing RPGs over FY 1996, and 743 total RPGs, an increase of 16 total RPGs over FY 1996.

Funds will be directed to the high priority areas of neuroscience research and understanding the role of brain functioning in the development and consequences of addiction, HIV/AIDS research and the relation of drug abuse as the primary vehicle for the transmission of HIV, the medications development program, behavioral research, and prevention research. As described earlier, the development of a medication for the treatment of cocaine addiction is the highest priority for the Institute in FY 1997.

In FY 1997, NIDA will be receiving \$2 million for each of the two NIH investment areas of the biology of brain disorders and new preventive strategies against disease.



NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse
Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
				Amount		Amount
Research grants:						
Research projects						
Noncompeting.....	469	\$123,662,000	531	\$135,503,000	525	\$128,922,000
Admin. supplementals.....	(27)	1,411,000	(12)	464,000	(12)	473,000
Competing						
Renewal.....	78	17,575,000	73	17,105,000	81	21,261,000
New.....	130	28,803,000	123	28,601,000	137	35,551,000
Subtotal, competing.....	208	46,378,000	196	45,706,000	218	56,812,000
Subtotal, res projects.	677	171,451,000	727	181,673,000	743	186,207,000
SBIR/STTR.....	29	4,519,000	26	5,514,000	28	6,877,000
Total, res projects.....	706	175,970,000	753	187,187,000	771	193,084,000
Research centers						
Specialized/comprehensive.....	21	22,741,000	21	23,764,000	22	24,359,000
Other research						
Research career program.....	111	11,348,000	102	11,872,000	104	12,072,000
Cooperative clinical res.....	2	1,024,000	2	1,414,000	2	1,414,000
Other research related.....	12	1,936,000	12	2,003,000	12	2,003,000
Subtotal, other res.....	125	14,308,000	116	15,289,000	118	15,489,000
Total, research grants.....	852	213,019,000	890	226,240,000	911	232,932,000

Training:

Individual awards						
Noncompeting.....	41	865,000	39	750,000	41	806,000
Competing.....	39	752,000	36	880,000	39	995,000
Subtotal, individual.....	80	1,617,000	75	1,630,000	80	1,801,000
Institutional awards						
Noncompeting.....	186	4,827,000	197	5,505,000	207	6,074,000
Competing.....	48	1,200,000	51	1,625,000	55	1,774,000
Subtotal, institutional.....	234	6,027,000	248	7,130,000	262	7,848,000
Total, training.....	314	7,644,000	323	8,760,000	342	9,649,000
Research and development contracts.....						
	70	25,181,000	70	27,523,000	67	26,596,000
Intramural research.....						
	FTEs		FTEs		FTEs	
	112	19,112,000	112	19,805,000	112	19,805,000
Res management and support.....	251	24,625,000	253	22,782,000	253	23,032,000
Total.....	363	289,581,000	365	305,110,000	365	312,014,000
		(28,786,000)		(29,300,000)		(29,900,000)
(Clinical Trials)						

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse
Budget Authority by Activity
(Dollars in thousands)

	1993 Actual		1994 Actual		1995 Actual		1996 Estimate		1997 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Drug abuse and addiction.....	--	\$233,962	--	\$239,064	--	\$245,604	--	\$262,523	--	\$269,177	--	+\$6,654
Intramural research.....	137	18,638	125	18,650	112	19,092	112	19,805	112	19,805	--	--
Research management and support.....	287	24,442	261	24,204	251	24,625	253	22,782	253	23,032	--	+250
Subtotal, obligations.....	424	277,042	386	280,918	363	289,321	365	305,110	365	312,014	--	+\$6,904
Unobligated balance lapsing.....	--	+94	--	+707	--	+260	--	--	--	--	--	--
Total, budget authority.....	424	277,136	386	281,625	363	289,581	365	305,110	365	312,014	--	+\$6,904

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTE OF HEALTH

National Institute on Drug Abuse

Summary of Changes

1996 Estimated budget authority.....	\$305,110,000
1997 Estimated budget authority.....	<u>312,014,000</u>
Net change.....	+ 6,904,000

Changes:	1996 Current	Change from Base
	Estimate Base	
	Budget	Budget
	FTE Authority	FTE Authority
A. Built-in:		
1. Intramural		
a. Within grade increase.....	\$7,460,000	+ 107,000
b. Annualization of		
January 1996 locality pay.....	7,460,000	+ 50,000
c. January 1997 pay increase.....	7,460,000	+ 178,000
d. Centrally furnished svcs.....	34,000	+ 24,000
e. Service and supply		
fund increase.....	6,363,000	+ 140,000
f. Increased cost of laboratory		
supplies, materials and other		
expenses.....	5,948,000	+ 131,000
Subtotal.....		+ 630,000
2. Research Management & Support		
a. Within grade increase.....	\$14,686,000	+ 266,000
b. Annualization of		
January 1996 locality pay.....	14,686,000	+ 97,000
c. January 1997 pay increase....	14,686,000	+ 347,000
d. Federal Employees Compen	14,686,000	+ 5,000
fund; unemployment comp		
e. Centrally furnished svcs.....	2,022,000	+ 9,000
f. Service and supply		
fund increase.....	4,545,000	+ 100,000
g. Increased cost of laboratory		
supplies, materials and		
other expenses.....	1,529,000	+ 33,000
h. Relocation expenses.....	6,074,000	+ 250,000
Subtotal.....		+ 1,107,000
Total Built-in		+ 1,737,000

Summary of Changes – con't

	1996 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
B. Program:				
	No.	Amount	No.	Amount
1. Research projects grants				
a. Noncompeting.....	531	135,967,000	-6	-6,572,000
b. Competing.....	196	45,706,000	22	+11,106,000
c. SBIRS.....	26	5,514,000	2	+1,363,000
Subtotal.....	753	187,187,000	18	+5,897,000
2. Research Centers.....	21	23,764,000	1	+595,000
3. Other Research.....	116	15,289,000	2	+200,000
Total, research grants.....	890	226,240,000	21	+6,692,000
4. Training.....	323	8,760,000	+19	+889,000
5. Contracts.....	70	27,523,000	-3	-927,000
6. Intramural research		19,805,000		-630,000
7. Research management & supp		22,782,000		-857,000
Subtotal				+5,167,000
Total changes.....				+6,904,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Authority by Object

	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>	<u>Increase</u> <u>or</u> <u>Decrease</u>
Total compensable workyears:			
Full-time equivalent employment.....	365	365	--
Full-time equivalent of overtime and holiday hours.....	2	2	--
Average ES salary.....	\$110,460	\$113,270	+ \$2,810
Average GM/GS grade.....	11.1	11.1	--
Average GM/GS salary.....	\$51,710	\$53,020	+ 1,310
Average salary, grades est by act of July 1, 1944 (42 USC 207).....	\$58,760	\$60,055	+ 1,295
Average salary of ungraded positions	\$58,600	\$59,700	+ 1,100
Personnel compensation:			
Full-time permanent.....	\$14,587,000	\$14,835,000	+ 248,000
Other than full-time permanent.....	1,813,000	1,837,000	+ 24,000
Other personnel compensation.....	367,000	323,000	-44,000
Special personnel services.....	<u>1,354,000</u>	<u>1,397,000</u>	<u>+ 43,000</u>
Subtotal, personnel compensation...	18,121,000	18,392,000	+ 271,000
Personnel benefits.....	3,954,000	3,990,000	+ 36,000
Benefits for former personnel.....	71,000	71,000	--
Travel and transportation of persons..	557,000	545,000	-12,000
Transportation of things.....	84,000	75,000	-9,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Rental payments to Others.....	71,000	71,000	—
Communications, Utilities..... and miscellaneous charges.....	2,076,000	2,073,000	-3,000
Printing and reproduction.....	662,000	652,000	-10,000
Other Services:			
Consultant Services.....	508,000	504,000	-4,000
Other Services.....	5,980,000	4,976,000	-1,004,000
Purchases from Govt. Accounts.....	9,130,000	10,201,000	+ 1,071,000
R&D Contracts.....	25,023,000	24,096,000	-927,000
Supplies and materials.....	2,033,000	2,002,000	-31,000
Equipment.....	1,840,000	1,785,000	-55,000
Grants, subsidies and contributions.....	<u>235,000,000</u>	<u>242,581,000</u>	<u>+ 7,581,000</u>
Total.....	305,110,000	312,014,000	+ 6,904,000

Note: Includes FTEs associated with HIV AIDS research activities. Funds to support these activities are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Administrative Costs

	1996 Estimate	1997 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1).....	\$14,587,000	\$14,835,000	+ \$248,000
Other than Full-time Permanent (11.3).....	1,813,000	1,837,000	+ 24,000
Other Personnel Compensation (11.5).....	367,000	323,000	-44,000
Special Personnel Serv. Payments (11.8).....	1,354,000	1,397,000	+ 43,000
Total Personnel Compensation (11.9).....	18,121,000	18,392,000	+ 271,000
Civilian Personnel Benefits (12.1).....	3,954,000	3,990,000	+ 36,000
Benefits to Former Personnel (13.0).....	71,000	71,000	0
Travel (21.0).....	557,000	545,000	-12,000
Transportation of Things (22.0).....	84,000	75,000	-9,000
Rental Payments to Others (23.2).....	71,000	71,000	0
Communications, Utilities and Miscellaneous Charges (23.3).....	2,076,000	2,073,000	-3,000
Printing and Reproduction (24.0).....	662,000	652,000	-10,000
Consulting Services (25.1).....	508,000	504,000	-4,000
Other Services (25.2).....	5,980,000	4,976,000	-1,004,000
Purchases from Government accounts (25.3)	2,405,000	2,345,000	-60,000
Supplies and Materials (26.0).....	1,983,000	1,952,000	-31,000
TOTAL.....	36,472,000	35,646,000	-826,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

SIGNIFICANT ITEM IN SENATE
APPROPRIATIONS COMMITTEE REPORT1996 Senate Report LanguageItem

Comprehensive Research Centers - ... The Senate in its report 104-145, page 99, stated: "...The Committee understands that NIDA has conducted a comprehensive review of its center grant program which will result in the publication of NIDA-wide center grant guidelines. The Committee continues to strongly encourage NIDA to support up to five multi-disciplinary, comprehensive drug abuse research centers to demonstrate the effectiveness of a variety of coordinated approaches focussed on women, children, minorities, or other underserved populations. Centers should provide a stable environment for investigators from biomedical, behavioral, and/or social sciences to conduct coordinated and integrated basic and clinical research and research training related to drug abuse. The Committee requests that NIDA be prepared to report on its center grant program during the 1997 appropriations hearings.

Action Taken or to be Taken

In December 1995 NIDA issued "Research Center Program Guidelines". The guidelines seek to ensure that the maximum scientific and programmatic benefits are being gained by the use of this grant mechanism. The new NIDA center guidelines emphasize the role of centers to foster inter-and multi-disciplinary collaborations and require center grant applications to demonstrate that the center has the potential to become a significant regional or national scientific resource. The center guidelines also established a new funding mechanism for identifying comprehensive research center grants.

NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse
Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Budget Request
Research and Investigation.....	Section 301	42 Sec 241	Indefinite		Indefinite	
National Institute on Drug Abuse.....	Title IV, Part C	42 Sec 285	Such sums as necessary	\$296,350,000	Indefinite	\$302,365,000
Medication Development.....	Section 464P	42 Sec 285o-4			Indefinite	
National Research Service Awards.....	Section 487(D)	42 Sec 298(d)	Such sums as necessary	8,760,000	Authorization Pending	9,649,000
Total Budget Authority.....				305,110,000		312,014,000

NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse
Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u>	<u>1/</u>
1993	N/A	N/A	\$410,502,000	\$403,806,000	2/
1994	\$407,098,000	\$425,201,000	425,201,000	425,201,000	
1995 3/ Rescission	291,963,000	290,280,000	290,280,000	289,581,000	4/
1996	298,738,000 3/	458,441,000	294,705,000 3/	-212,000 458,441,000	
1997 3/	312,014,000				

N/A = Not Applicable.

1/ Reflects enacted supplementals, rescissions, reappropriations and reductions. Prior to the FY 1993 Senate Allowance, NIDA was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of \$3,272,000, \$430,000, and \$1,474,000.

3/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

4/ Excludes enacted administrative reduction of \$39,000.

NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse
Detail of Full-Time Equivalent Employment

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	16	16	16
Office of Planning & Resource Management.....	60	56	56
Office of Extramural Program Review.....	29	26	26
Office on AIDS.....	3	3	3
Division of Basic Research.....	22	25	25
Division of Clinical & Services Research.....	30	32	32
Division of Epidemiology & Prevention.....	28	30	30
Office of Science Policy & Communications.....	29	29	29
Medications Development Division....	34	36	36
Addiction Research Center.....	112	112	112
Total, NIDA.....	363	365	365
Average GS/GM Grade			
1992.....	10.7		
1993.....	10.9		
1994.....	10.9		
1995.....	11.1		
1996.....	11.1		
1997.....	11.1		

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse
Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Request
ES-6.....	1	1	1
ES-5.....	1	1	1
ES-4.....	4	4	4
ES-2.....	1	1	1
Subtotal.....	7	7	7
Total - ES Salary.....	754,100	773,250	792,890
CS/GM-15.....	40	40	40
CS/GM-14.....	68	69	69
CS/GM-13.....	41	42	42
CS-12.....	32	34	34
CS-11.....	20	21	21
CS-10.....	2	2	2
CS-9.....	10	10	10
CS-8.....	13	13	13
CS-7.....	33	33	33
CS-6.....	22	22	22
CS-5.....	8	8	8
CS-4.....	11	11	11
CS-3.....	2	2	2
CS-2.....	2	2	2
Subtotal.....	304	309	309
Grades established by Act of July 1, 1944 (42 U.S.C.207):			
Director Grade.....	17	17	17
Senior Grade.....	4	4	4
Full Grade.....	3	3	3
Senior Assistant Grade.....	1	1	1
Subtotal.....	25	25	25
Ungraded.....	28	24	24
Total permanent positions.....	53	49	49
Total positions end of year.....	364	365	365
Total full-time equivalent (FTE) employment, end of year.....	363	365	365
Average ES level.....	4.1	4.1	4.1
Average ES salary.....	107,729	110,460	113,270
Average GS/GM grade.....	11.1	11.1	11.1
Average GS/GM salary.....	50,425	51,710	53,020

JUSTIFICATION OF THE BUDGET ESTIMATES

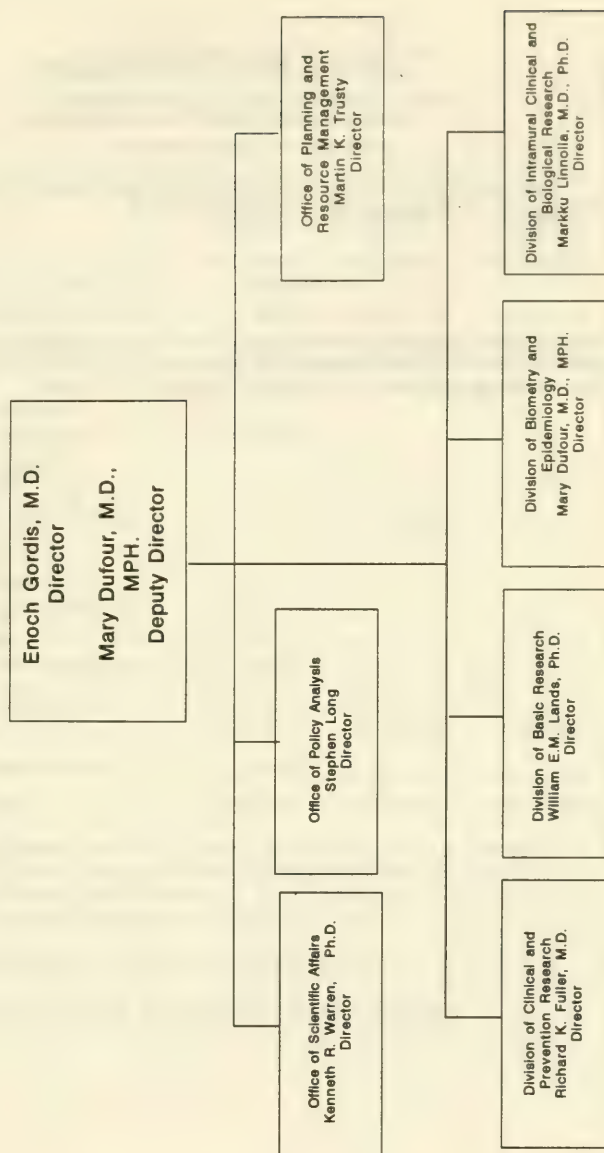
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

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NATIONAL INSTITUTES OF HEALTH National Institute on Alcohol Abuse and Alcoholism Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

For carrying out section 301 and title IV of the Public Health Service Act with respect to alcohol abuse, and alcoholism, [\$188,472,000] \$198,280,000.

Note - A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$181,445,000	\$198,607,000	\$192,280,000
Enacted reduction P.L. 103-333.....	-189,000 2/	---	---
Enacted rescission, P.L. 104-19.....	-106,000	---	---
Subtotal, adjusted appropriation	181,150,000	198,607,000	192,280,000
Real transfer to:			
Other NIH Institutes for NIH Director's initiatives.....	-156,000		
Comparative transfer to:			
Office of AIDS Research, NIH for HIV/AIDS activities.....	---	-10,135,000	
Comparative transfer to:			
Other NIH Institutes for Management Fund adjustment.....	-844,000		
Comparative transfer to:			
NIH/OD for accounting charges.....	-86,000		
Subtotal, adjusted budget authority.....	180,064,000	188,472,000	192,280,000
Unobligated balance, lapsing.....	-187,000	---	---
Total obligations.....	179,877,000	188,472,000	192,280,000

1/ Excludes the following amounts for reimburseable activities carried out under this account: FY 1995 - \$2,669,000; FY 1996 - \$2,215,000; FY 1997 - \$2,215,000.
Also excludes funding for HIV activities: FY 1995 - \$9,741,000;
FY 1997 - \$10,334,000 to the Office of AIDS Research, NIH.

2/ Includes reductions for procurement, SLUC, and bonus pay.

Note: Excludes \$3,768 in FY 1995 and \$6,500 in FY 1996 for royalties.

Justification

National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation: Public Health Service Act, Title III, Part A Section 301, Title IV, Part C Sections 464H and 487.

Budget Authority:

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
222	\$180,064,000	223	\$188,472,000	223	\$192,280,000	--	+\$3,808,000

General Statement**MISSION**

This document provides justification for FY 1997 Non-AIDS activities of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled, "Office of AIDS Research (OAR)".

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the foremost Federal agency supporting biomedical and behavioral research directed towards improving the prevention and treatment of alcohol abuse and alcoholism and reducing associated health, economic, and social consequences. NIAAA provides leadership in the country's effort to combat these problems, by developing new knowledge that will decrease the incidence and prevalence of alcohol abuse and alcoholism, and associated morbidity and mortality.

RESEARCH STORY

Fetal Alcohol Syndrome (FAS) is a serious disorder with physical and mental deficiencies that are costly to treat and rehabilitate and which often require long-term care. Since 1972, the NIAAA has supported a broad range of research on the epidemiological, biomedical, and behavioral aspects of FAS and the lesser effects of alcohol-related birth defects. Prior to 1973 the cause of mental and physical defects seen in some babies was unknown. NIH-funded research provided the earliest evidence of FAS by showing birth defects in the offspring of rodents that were fed alcohol during their pregnancy. In 1973-74, investigators reported clusters of specific birth defects appearing in infants born to mothers who abused alcohol during their pregnancy. The full syndrome is characterized by prenatal and postnatal growth retardation, a characteristic constellation of craniofacial anomalies, central nervous system dysfunctions and major organ system malformations.

By 1977 researchers had demonstrated that: 1) alcohol is a physical and behavioral teratogen (causes abnormal fetal development resulting in physical and behavioral abnormalities); 2) *in utero* alcohol exposure can produce a spectrum of deleterious effects; and 3) FAS is 100 percent preventable through abstinence from alcohol consumption during pregnancy. Based on this information, NIAAA prepared and distributed more than 200,000 copies of its first "Health Caution" to hospitals, clinics, public health workers, and other health care professionals. This public health announcement, based on NIAAA-supported research, was the first of its kind to describe the link between alcohol and birth defects and to advise caution to pregnant women.

Although it was clear that there was a health risk to children when mothers drank heavily during pregnancy, the level of risk could not yet be correlated with an actual amount of consumption. While research on this important facet continued, NIAAA and FDA collaborated on devising an appropriate warning label to be placed on alcohol beverages. The March of Dimes distributed 15,000 copies of NIAAA's publication, "Preventing Fetal Alcohol Effects: Practical Guide for OB/GYN Physicians and Nurses," to help medical professionals identify alcohol-abusing patients. Federally issued Dietary Guidelines for Americans stated that "Sustained or excessive alcohol consumption by pregnant women has caused birth defects. Pregnant women should limit alcohol intake to 2 ounces or less on any single day." In 1981 the Surgeon General issued an advisory to health professionals on alcohol and pregnancy and urged them to routinely inquire about alcohol consumption by pregnant patients, to inform their patients of the risks associated with alcohol consumption during pregnancy, and to advise their patients not to drink alcoholic beverages while pregnant.

Investigators continued efforts to accurately describe the effects of *in utero* alcohol exposure on newborns and developing children. NIAAA-supported researchers began characterizing the nature and potential of alcohol-related birth defects in animal models and in humans. Children with alcohol-related birth defects were frequently described as hyperactive, distractable, impulsive, and as having short attention spans. These behaviors were similar to those observed in children with attention deficit disorder (ADD). Understanding the differences and similarities between FAS and ADD children is important for the design of effective treatments.

By 1984, researchers demonstrated that FAS children are more intellectually impaired (as measured by IQ tests) than children with ADD. Researchers proposed that treatment strategies developed for ADD might benefit children with alcohol-related birth defects as well. An NIAAA-funded demonstration program became a model for public and professional education on FAS, clinical services for pregnant women, assessment services for children with FAS, and program evaluation.

The costs of FAS and related conditions can be quite high -- for the individual, for the family, and for society. Economic studies show far-reaching effects connected with alcohol-related birth defects. By 1990, that figure was estimated to be \$2.1 billion.

During the time period 1985-1988, NIAAA sharply increased the number of research grants looking at the teratogenic effects of alcohol. New federal dietary guidelines recommended that mothers abstain from alcoholic beverages during pregnancy, particularly because the exact level of alcohol required to cause damage was unknown. In 1988, as a direct result of NIAAA-

supported research, a law was enacted requiring labels on all alcoholic beverages that warned of the dangers associated with drinking during pregnancy and drinking and driving.

Alcohol is one of a number of chemical compounds that are toxic to the developing central nervous system of humans. The neurotoxic properties of alcohol have been well studied in animal models. Of all drugs of abuse, including heroin, cocaine, and marijuana, misuse of alcohol produces by far the most serious neurobehavioral effects in the fetus. Throughout gestation, the fetus is in a continual state of orderly biochemical and structural transitions during which new tissues are being formed and spatially rearranged. At any time in the total span of development, these ongoing processes can be subtly deflected, severely perturbed, or abruptly halted. Alcohol causes the characteristic features of FAS, craniofacial defects of the eyes, upper lip, and jaw, arising from improper development of the cranial neural crest during embryogenesis. The effects of alcohol exposure during specific stages or "critical periods" of development are probably best documented for its anatomical or dysmorphic effects (malformation, disruption, and deformation).

The human experience with exposure to alcohol during pregnancy corroborates some of the central developmental concepts provided by animal research. These concepts include: diversity in the degree of injury to fetuses with comparable alcohol exposure; the potential for injury throughout fetal life; a relationship between level of alcohol exposure and degree of injury; and the importance of both biological variables and the postnatal environment in influencing outcome. Data on the effects of alcohol exposure on infant growth and functional deficits are also increasing. In 1995, a trans-NIH interest group focusing on the teratology of alcohol was established by NIAAA to improve communication and collaboration on FAS and FAS-related research.

Although much progress has been made in elucidating the underlying mechanisms of FAS and in characterizing fetal outcomes, NIAAA remains committed to furthering our understanding of the effects of alcohol on fetuses and children. For instance, the recently completed National Academy of Sciences, Institute of Medicine study of FAS recommends: to relate neurological abnormalities and other neurobiological indices to cognitive and behavioral correlates; to conduct further clinical research that examines the adverse developmental effects of prenatal alcohol exposure; to develop more specific biological markers for diagnosis; and to consider the potential role of fetal alcohol exposure, as appropriate, in developmental disability studies in general. NIAAA's portfolio already reflects many of these priorities. For instance, research to elucidate the underlying cellular and molecular mechanisms of ethanol-induced fetal injury, particularly in the developing nervous system, is supported. Basic approaches include the use of appropriate *in vivo* animal models, including transgenic animals and recombinant inbred lines, cell culture techniques, molecular biology, and behavioral techniques to correlate biochemical events with cognitive and behavioral deficits.

Although we have made substantial progress in the past 25 years, much work remains. Areas of further interest include the role of oxidative stress in ethanol-induced disruption of developmental processes; perturbations of signal transduction systems that regulate development; alterations in neurotrophic factors, morphogen, and extracellular matrix protein dynamics that are critical for cellular growth and differentiation; and the interactions of ethanol

and transcription factors such as retinoic acid in the control of gene expression during development and differentiation of susceptible cell populations. As our understanding of the underlying molecular mechanisms of damage progresses, studies to develop and test therapeutic interventions in utero and postnatally will be supported.

Studies are needed to elucidate risk factors that contribute to increased susceptibility to fetal injury. Research opportunities include linking specific cognitive and behavioral deficits to in utero patterns of exposure and ethanol dose, identification of critical periods of in utero exposure for susceptible cell populations, identification of biochemical markers uniquely linked to maternal ethanol consumption or exposure of the fetus to ethanol, and genetic studies to identify genes that confer differential susceptibility to FAS. Research areas needing attention include the interaction of maternal ethanol and stress on the maternal neuroendocrine axis, regulation of nutrient uptake and utilization by the placenta and fetus, and perturbations of vascular homeostasis in the feto-placental unit.

Research in these areas promises to provide the data needed to develop therapies for ameliorating the effects of alcohol on the fetus; developing methods of identifying those women most at risk; and developing appropriate interventions.

OTHER BENEFITS OF RESEARCH

♦ BIOLOGY OF BRAIN DISORDERS

Alcohol, after ingestion, is distributed to every cell in the body. Yet it produces very specific effects: motor impairment, memory loss, and the possible development of alcohol addiction, or alcoholism. Our main problem in neuroscience, then, is to understand which brain cells, neurotransmitters, and connected neurons (neural circuits) account for the specific action of alcohol and the symptoms of alcoholism: physical dependence, tolerance, loss of control of drinking, and the craving for alcohol seen in sober alcoholics which leads to relapse. All these issues are now approached with cutting edge technology. Cell receptor systems (for example, serotonin, GABA, NMDA) have been identified which vary only minimally. Although the variation is small, the effects are major among strains of animals raised to demonstrate different effects of alcohol. We propose to precisely understand these receptor differences by developing antibodies to the subsets of these receptors. This will allow us to determine which receptor subsets are most sensitive to alcohol. We will also expand our use of transgenic animals which have been bred with different brain receptor structures to determine which constitute the most vulnerable systems to alcohol. Newer techniques make it possible to create transgenic animals whose genetic differences are limited only to the brain, thus eliminating unwanted changes in other tissues. Our intramural scientists are conducting complementary research on brain neurotransmitter functions by studying the cerebral spinal fluid of alcoholic criminal offenders and normal volunteers; genetic transmission and linkage analysis is being done in large American Indian families with alcoholism.

Advances in predicting who will be at high-risk for alcohol abuse disorders (i.e., determining vulnerability) so that preventive interventions can be specifically tailored and directed is a high priority at NIAAA. Earlier work demonstrated that the risk of developing alcoholism is

correlated with family history. Fresh hope of identifying those most at risk before the onset of alcoholism rests on longitudinal studies of children whose brain waves have been scientifically analyzed.

A considerable body of evidence suggests that brain neuroelectrical activity (brainwaves), including event-related potentials (ERPs), is heritable. Recently, ERP data from one of NIAAA's large family studies of alcoholism has been analyzed by segregation analysis to determine possible modes of inheritance of the P300 component of ERPs. There is evidence for a major gene controlling the familial similarity found in P300 amplitude. If future studies confirm these findings in larger sample sizes, clinicians will have a biological marker for identifying individuals, as well as groups, who are at greatest risk of developing alcoholism. This heralds an opportunity to break the intergenerational cycle in families predisposed to developing alcoholism.

◆ GENETICS

The NIAAA is coordinating a major multi-disciplinary, collaborative research study (COGA) on the genetics of alcoholism. The project involves six research institutions throughout the Nation and is resolving the genetic factors that determine vulnerability to alcoholism. COGA is a pedigree study that uses molecular genetic techniques to establish the genetic typing of a total of 2,400 individuals comprising several hundred families in which alcoholism is multiply represented. Enrollment of families and data collection are nearly complete, and investigators are preparing to analyze the first wave of genotyping. We are approaching the final stage of this research, linkage analysis. Linkage study methods are evolving rapidly based on the human genome project and improvements in statistical methods.

In 1996 NIAAA made several new awards for quantitative trait loci (QTL) mapping. QTL mapping is a promising technique that relates complex behavioral traits to specific genes. Some alcohol-related genes have been roughly mapped in mice. This mapping provides clues on the location of corresponding genes in humans. In 1997, we are proposing to increase the scope of the 1996 RFA on QTL mapping. The next step is to map the location of genes more precisely, isolate the genes, and identify their protein products. We are also recruiting additional investigators in this promising and exciting area.

A complementary approach to QTL mapping is mutagenesis screening in mice. This procedure uses chemical mutagens to induce mutations artificially in strains of mice. Mutations of interest will cause mice to exhibit altered alcohol-related behaviors. Researchers can then use powerful methods of Mendelian and molecular genetics to map the mutated genes precisely, isolate them, and determine the products they encode. This approach is an efficient, direct method for discovering the genes that determine vulnerability to alcohol. NIAAA plans to use methods developed by other investigators to produce mutant mice with greatly altered circadian rhythms. NIAAA will issue an RFA in 1997 to encourage investigators to apply mutagenesis screening to mice to identify alcohol-related traits.

♦ PATHOGENESIS

Promising Therapeutic Strategies for the Treatment of Liver Disease

A recent NIAAA study provides a potential new strategy for the prevention and clinical management of alcohol-related liver disease. Millions of patients worldwide suffer from alcohol-induced liver disease as a result of excess consumption of alcoholic beverages. Alcoholic liver disease is the fourth major cause of death in men in the urban U.S. and costs the Nation between 3-5 million dollars annually. Treatment efforts are largely ineffective, partly because the exact mechanisms of liver damage promoted by alcohol are unknown and cirrhosis is irreversible. This study represents a significant intellectual change in the approach to treating alcohol-related liver disease. NIAAA-supported investigators demonstrated that treatment with the antibiotics polymyxin B and neomycin which target intestine-derived endotoxin producing bacteria prevented alcohol-induced liver injury in the rat model. This treatment also prevented alcohol-induced hypoxia and increases in rates of alcohol elimination (hypermetabolism). This supports the hypothesis that hypermetabolism and consequent hypoxia caused by activation of Kupffer's cells (special phagocytic liver cells) by endotoxin is involved in the mechanism of alcohol-induced liver disease. This study suggests that clinical management of alcohol-induced liver injury may be improved by reducing the number of gram-negative bacteria producing endotoxin in the intestine.

♦ POTENTIAL MECHANISMS OF ALCOHOL-RELATED TISSUE INJURY

NIAAA has been capitalizing on the exciting momentum generated by recent advances in understanding potential mechanisms of alcohol-related tissue injury. There is a large collection of substances called cytokines that play a vital role in coordinating immune and inflammatory responses to toxins, such as alcohol. Among these cytokines are nuclear factor kappa B (NFkB), cytokines, tyrosine phosphates, and reactive oxygen species, which act in concert to promote alcohol-related tissue injury. Normal cellular proliferation and differentiation requires an intricate balance among many different cytokines. Alcohol interferes with normal mechanisms of controlling cellular proliferation and differentiation. When this intricate balance is disrupted, the normal ebb and flow of cellular proliferation and differentiation is altered leading to inflammatory responses. Thus the orderly pattern of growth and differentiation is unsettled and untimely and inappropriate cell death may occur (necrosis).

This cell death can lead to signal cascades and feedback loops which result in further tissue injury. For instance, alcohol-related liver disease results from the interaction of alcohol with an intricate web of interactive intracellular and intercellular signals. Important cellular players include hepatocytes, Kupffer cells, Ito cells, monocytes, neutrophils, and endothelial cells. Changes in the abundance and function of these cells and their matrices within the liver constitute progressive liver pathology. Understanding these changes requires further study to elucidate how these cells and their signals interact to cause slow cumulative changes in the liver from normal tissue to alcohol-induced diseased tissue.

In addition to causing liver disease, alcohol causes perturbations in immune functioning, glucose regulation, and alcohol-related cellular dysfunctions. Chronic alcohol exposure may

lead to alcohol-induced insulin resistance, a condition in which the body is unable to properly respond to insulin. NIAAA is committed to increasing research on the effects of alcohol on cellular signaling and interactions. In 1996 workshops at the National Research Society on Alcohol were held in each of these areas. Workshops are excellent venues for stimulating investigator initiated grant applications in specific areas. Understanding the intricacies of inter- and intracellular communication promises to yield exciting new therapies which will enhance quality of life and reduce health care costs.

Another avenue of research is exploring the role of the principal nervous system polyunsaturated fatty acid, docosahexaenoic acid (DHA). It has become increasingly clear that DHA is important for optimal brain development. A deficiency in DHA may also occur in adults on very low fat diets or those who abuse alcohol. Intramural studies indicate that diets very low in DHA precursors can lower brain DHA in primates. Chronic alcohol intake further exacerbates this loss. Many alcoholics have a poor diet and suffer from losses in antioxidant vitamins, such as vitamin E. Low essential fatty acid intake coupled with alcohol leads to losses in brain DHA, and may affect many of the Nation's 13 million alcoholics. An important public health benefit may result if future research shows that dietary supplementation with DHA results in less alcohol-induced brain and liver pathology. The significance of DHA is not only evident in the alcohol field, but it may also have a potential impact in other areas of research as well.

♦ **TREATMENT FOR ALCOHOLISM**

Naltrexone was recently approved by the FDA for the treatment of alcoholism. In clinical trials, naltrexone was shown to be very effective in reducing both alcohol craving and alcohol consumption. Naltrexone is a medication that binds to the body's naturally occurring opiate receptors and its use in alcoholism treatment is a direct result of advances in our understanding of neuroscience. Alcoholics treated with naltrexone experienced fewer days drinking, had less craving for alcohol, a smaller number of heavy drinking episodes, and less alcohol use after relapse. In fact, recent studies indicate that significantly fewer patients treated with naltrexone returned to heavy drinking compared with those treated with placebo. Another new drug, acamprosate, is currently being tested in clinical trials in Europe with promising results. Upon its approval for investigation in the U.S., NIAAA will be prepared to help organize trials with acamprosate.

A variety of other promising medications are also being tested throughout the U.S. The selection of these medications is also based on increased understanding of neuroscience. Clinical trials are underway that are examining the efficacy of fluoxetine and sertraline, both antidepressants and serotonin re-uptake inhibitors, on alcoholics with collateral major depression. Improvements in several outcome measures are being evaluated including frequency and intensity of drinking and severity of psychiatric disorder. In addition to their antidepressant actions, serotonin re-uptake inhibitors have also shown a direct effect in reducing drinking. We are also pursuing an interagency agreement to synthesize a metabolite of disulfiram (antabuse). This metabolite is 40 times more potent than disulfiram; thus less of it is needed and side effects are diminished.

In the future, advances in understanding brain neurochemistry and physiology, particularly the biological bases for alcohol use and the phenomenon of craving, will provide new pharmacotherapeutic possibilities. Development of new medications to prevent relapse to alcoholic drinking will have a major positive impact on the effectiveness of treatment for alcoholism. It is expected that advances in treatment will ultimately reduce the cost of health care. These leads hold exciting promise for alleviating the suffering caused by alcohol abuse and alcoholism.

◆ PREVENTION STRATEGIES

NIAAA maintains an active portfolio in the area of prevention. The goal of NIAAA-sponsored prevention research is to obtain scientifically objective and measurable effects attributable to specific interventions. To ensure the acquisition of meaningful results that are generalizable to other locations, these studies employ rigorously defined scientific methodologies including random selection and control communities. NIAAA has a history of effectively contributing to the formulation of public policy. In addition to its contributions in preventing fetal alcohol syndrome, NIAAA research has contributed scientifically derived data to the public debate concerning the legal drinking age which is now 21 in all states.

A recent NIAAA-sponsored study is a good example of the contribution of science to the formulation of public policy. The data show that lowering the legal blood alcohol limit (BAL) for young drivers reduced fatal single vehicle nighttime crashes (the type of crash most likely to involve alcohol) among adolescents and that the lower the limit is set, the greater the reduction. This study, and one other NIAAA-funded study, provided the data that led to the enactment by Congress of "federal incentive" legislation to encourage all states to pass zero tolerance laws specifying a maximum legal BAL limit of 0.02 for youth younger than 21. The President signed the act into law on November 28, 1995. NIAAA-supported investigators are continuing to add to our knowledge base about effective prevention strategies by supporting community trials, analysis of family interactions, and drinking and driving interventions. Alcohol abuse and alcoholism costs the Nation \$98 billion dollars annually in direct and indirect costs, and untold human anguish. Prevention of problems associated with excess alcohol use promises substantial reductions in cost and human suffering.

The President's appropriation request of \$192,280,000 for this account represents current law requirements. No proposed law amounts are included.

Overall Budget Policy

The FY 1997 request for NIAAA is \$192,280,000, an increase of \$3,808,000 or 2.0 percent over the FY 1996 estimate of \$188,472,000.

In the FY 1997 President's Budget Request, NIAAA support for research project grants (RPGs) would increase by 4.3 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7

percent for the Biomedical Research and Development Price Index. Thus, in FY 1997 noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 112 competing RPGs and 472 total RPGs, an increase of 15 total RPGs over FY 1996.

A total of 13 research centers would be supported in the FY 1997 request at \$19,490,000, the same level as FY 1996.

Other research grants would be supported at \$13,548,000, a 2.2 percent reduction from the 1996 estimate. This includes 50 research careers at \$4,674,000; \$7,888,000 for the Cooperative Agreements; \$321,000 for Minority Biomedical Research Support; and \$665,000 for 2 awards comprised of science education awards and scientific evaluation grants.

The FY 1997 request would support 192 full-time training positions at \$5,375,000, an increase of two training positions over the FY 1996 estimate and a funding increase of \$102,000. A stipendary increase of 2 percent would be provided.

Research and development contracts would be supported at \$8,018,000, a reduction of \$572,000 from the 1996 estimate.

The FY 1997 request includes \$20,115,000 for intramural research and \$12,041,000 for research management and support, approximately the same level as the FY 1996 estimate. In FY 1997, 223 FTEs are requested, the same number included in the 1996 estimate.

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism
Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects						
Noncompeting.....	304	\$70,611,000	313	\$78,182,000	350	\$86,379,000
Administrative supplementals.....	(32)	974,000	(19)	889,000	(19)	889,000
Competing:						
Renewal.....	32	8,537,000	40	8,480,000	36	7,920,000
New.....	112	20,181,000	92	19,411,000	74	15,913,000
Supplemental.....	2	545,000	2	400,000	2	400,000
Subtotal, competing.....	146	29,263,000	134	28,291,000	112	24,233,000
SBIR/STTR.....	11	1,349,000	10	1,691,000	10	2,192,000
Subtotal, research projects.....	461	102,197,000	457	109,053,000	472	113,693,000
Research Ctrs:						
Specialized/comprehensive.....	13	18,417,000	13	19,490,000	13	19,490,000
Other Research:						
Research career program.....	44	4,035,000	50	4,674,000	50	4,674,000
Cooperative clinical research.....	12	8,556,000	12	8,505,000	11	7,888,000
Minority biomedical research sup	--	275,000	--	321,000	--	321,000
Other research related.....	4	381,000	2	360,000	2	665,000
Subtotal, other research.....	60	13,247,000	64	13,860,000	63	13,548,000
Total, research grants.....	534	133,861,000	534	142,403,000	548	146,731,000

Training:						
Individual awards:						
Noncompeting.....	24	460,000	26	462,000	21	291,000
Competing.....	20	382,000	13	322,000	20	551,000
Subtotal, individual.....	44	842,000	39	784,000	41	842,000
Institutional awards:						
Noncompeting.....	116	2,906,000	151	4,489,000	111	3,342,000
Competing.....	48	1,422,000			40	1,191,000
Subtotal, institutional.....	164	4,328,000	151	4,489,000	151	4,533,000
Total, training.....	208	5,170,000	190	5,273,000	192	5,375,000
Research and development contracts						
SBIR/STTR.....	20	8,875,000	28	8,590,000	28	8,018,000
	(5)	(1,847,000)	(5)	(1,780,000)	(5)	(1,780,000)
	FTEs		FTEs		FTEs	
Intramural research.....	93	19,141,000	90	20,165,000	90	20,115,000
Research management and support.....	129	13,017,000	133	12,041,000	133	12,041,000
Total.....	222	180,064,000	223	188,472,000	223	192,280,000
Clinical trials.....		(16,975)		(18,000)		(18,500)

Includes 6 FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Activity
(Dollars in thousands)

	1993 Actual		1994 Actual		1995 Actual		1996 Estimate		1997 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research												
Alcohol biomedical and behavioral research.....	--	\$136,440	--	\$142,990	--	\$147,799	--	\$156,266	--	\$160,124	--	+\$3,858
Intramural research.....	112	19,991	101	19,311	93	19,106	90	20,165	90	20,115	--	-50
Research management and support.....	142	12,919	133	12,864	129	12,972	133	12,041	133	12,041	--	0
Sub-total obligations.....	254	169,350	234	175,165	222	179,877	223	188,472	223	192,280	--	+3,808
Unobligated balance, lapsing.....	--	273	--	78	--	187	--	--	--	--	--	--
Total budget authority....	254	169,623	234	175,243	222	180,064	223	188,472	223	192,280	--	+3,808

National Institute on Alcohol Abuse and Alcoholism

Summary of Changes

1996 Estimated budget authority.....	\$ 188,472,000
1997 Estimated budget authority.....	192,280,000
Net change.....	+ 3,808,000

Changes:	1996 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural Research				
a. Within grade increases.....		\$7,706,000		+\$98,000
b. Annualization of January, 1996 locality pay raise.....		7,706,000		+50,000
c. January, 1997 pay increases.....		7,706,000		+176,000
d. Unemployment compensation, Federal employees compensation fund increase.....		7,706,000		+1,000
e. Payment for centrally furnished services.....		5,912,000		-163,000
f. Service and Supply Fund increase.....		600,000		+34,000
g. Increased cost of supplies, materials and other expenses.....		5,947,000		+283,000
Subtotal.....				+479,000
2. Research Management and Support				
a. Within grade increases.....		8,982,000		+166,000
b. Annualization of January, 1996 locality pay raise.....		8,982,000		+58,000
c. January, 1997 pay increases.....		8,982,000		+206,000
d. Unemployment compensation, Federal employees compensation fund increase.....		8,982,000		+2,000
e. Payment for centrally furnished services.....		375,000		+26,000
f. Service and Supply Fund increase.....		700,000		+34,000

Summary of Changes-continued

	1996 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
g. Increased cost of supplies, materials and other expenses.....		2,184,000		+78,000
Subtotal.....				+570,000
Subtotal, built-in.....				+1,049,000
 B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a: Noncompeting.....	313	\$79,071,000	+37	+\$8,197,000
b: Competing.....	134	28,291,000	-22	-4,058,000
c: SBIR/STTR.....	10	1,691,000	—	+501,000
Subtotal.....	457	109,053,000	+15	+4,640,000
2. Research Centers.....	13	19,490,000	—	—
3. Other research.....	64	13,860,000	-1	-312,000
4. Research training awards.....	190	5,273,000	+2	+102,000
5. Research and Development Contracts.....	28	8,590,000	—	-572,000
	FTEs		FTEs	
6. Intramural Research.....	90	20,165,000	—	-529,000
7. Research Management and Support.....	133	12,041,000	—	-570,000
Subtotal, program.....				+2,759,000
Total changes.....				+3,808,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Object

	<u>1996 Estimate</u>	<u>1997 Estimate</u>	<u>Increase or Decrease</u>
Total compensable workyears:			
Full-time equivalent employment.....	223	223	---
Full-time equivalent of overtime and holiday hours.....	1	1	---
Average ES salary.....	\$129,100	\$129,100	---
Average GM/GS grade.....	10.9	10.9	---
Average GM/GS salary.....	\$49,876	\$50,125	+249
Average salary, grades est. by act of July 1, 1944 (42 USC 207).....	53,924	54,193	+269
Average salary of ungraded positions.....	43,385	43,600	+215
Personnel compensation:			
Full-time permanent.....	\$10,000,000	\$10,014,000	+\$14,000
Other than full-time permanent.....	1,519,000	1,612,000	+93,000
Other personnel compensation.....	431,000	439,000	+8,000
Special personnel services.....	1,664,000	1,669,000	+5,000
Total personnel compensation.....	13,614,000	13,734,000	+120,000
Personnel benefits.....	3,063,000	2,916,000	-147,000
Benefits for former personnel.....	11,000	35,000	+24,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Travel and transportation of persons.....	226,000	243,000	+17,000
Transportation of things.....	84,000	54,000	-30,000
Rental payments to GSA.....	1,456,000	1,516,000	+60,000
Rent, communications and utilities.....	720,000	841,000	+121,000
Printing and reproduction.....	361,000	314,000	-47,000
Other Services:			
Consulting services.....	53,000	55,000	+2,000
Other Services.....	3,655,000	3,057,000	-598,000
Purchases from Govt. Accts.....	6,636,000	6,894,000	+258,000
Operation of GOCOs.....	53,000	54,000	+1,000
R&D Contracts.....	8,590,000	8,018,000	-572,000
Supplies and materials.....	1,594,000	1,737,000	+143,000
Equipment.....	618,000	644,000	+26,000
Grants, subsidies and contributions.....	147,676,000	152,106,000	+4,430,000
Insurance Claims & Indemnities.....	62,000	62,000	- - -
Total, budget authority by object.....	188,472,000	192,280,000	+3,808,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

	Administrative Costs		
	1996 Current Estimate	1997 Estimate	Change
Personnel Compensation			
Full-time permanent (11.1).....	\$10,000,000	\$10,014,000	+\$14,000
Other than Full-time Permanent (11.3)..	1,519,000	1,612,000	+93,000
Other Personnel Compensation (11.5)...	431,000	439,000	+8,000
Special Personnel Services (11.8).....	1,664,000	1,669,000	+5,000
Total Personnel Compensation (11.9).	13,614,000	13,734,000	+120,000
Civilian Personnel Benefits (12.1).....	3,063,000	2,916,000	-147,000
Benefits to Former Personnel (13.0).....	11,000	35,000	+24,000
Travel (21.0).....	226,000	243,000	+17,000
Transportation of Things (22.0).....	84,000	54,000	-29,000
Communications, Utilities, and Miscellaneous Charges (23.3).....	720,000	841,000	+121,000
Printing and Reproduction (24.0).....	361,000	314,000	-47,000
Consulting Services (25.1).....	53,000	55,000	+2,000
Other Services (25.2).....	3,655,000	3,057,000	-598,000
Purchases from Govt. Accts. (25.3).....	6,636,000	6,894,000	+258,000
Operation of GOCOs (25.4).....	53,000	54,000	+1,000
Supplies and Materials (26.0).....	1,594,000	1,737,000	+143,000
Total Obligations (99.0).....	30,070,000	29,934,000	-135,000

National Institute on Alcohol Abuse and Alcoholism

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Genetics - The Committee recognizes that significant strides have been made in recent years in research on genetic bases for a wide range of medical conditions and funds that such research has great promise in the area of alcohol abuse and alcoholism. The Committee encourages to enhance its research into genetic bases for alcohol abuse and alcoholism.

Action Taken or to be Taken

NIAAA's Collaborative Research Study on the Genetics of Alcoholism is progressing extremely well. The first wave of genotyping is nearly complete and we are approaching the final stage of this research. Nearly 7500 interviews of alcoholics and their family members have been conducted. Cell lines from 2344 individuals belonging to 269 families are available for genetic analysis. Genetic marker typing of the first group of 990 subjects and collection of approximately 300 markers spanning the entire genome is about 70% completed. In 1996 NIAAA made several new awards for quantitative trait loci (QTL) mapping which is a promising technique that relates complex behavioral traits to specific genes. This approach is an efficient, direct method for discovering the genes that determine vulnerability to alcohol.

Item

Medications Development - The Committee is pleased that research supported by NIAAA has led to the approval of naltrexone by FDA for alcoholism treatment. The Committee encourages NIAAA to support further research to determine the effects of naltrexones longer-term use, side effects, and how it reduces alcohol craving.

Action Taken or to be Taken

Alcoholics treated with naltrexone experienced fewer days drinking, had less craving for alcohol, a smaller number of heavy drinking episodes, and less alcohol use after relapse. In fact, recent studies indicate that significantly fewer patients treated with naltrexone returned to heavy drinking compared with those treated with placebo. NIAAA-sponsored clinical trials are now determining which groups of patients are most responsive to this medication. The benefits and side effects of long-term use of naltrexone are also under investigation. Another new drug, acamprosate, is currently being tested in clinical trials in Europe with promising results. Upon its approval for investigation in the U.S., NIAAA will be prepared to help organize trials with acamprosate.

Item

Moderate Drinking - The Committee notes favorably that NIAAA has publicized its intention to support research on the health effects of moderate wine and alcohol consumption at a significant funding level. The Committee urges NIAAA and other Institutes to support and assist research efforts in these areas, especially the impact of alcohol on cardiovascular health and longevity and on the dietary role of antioxidants and moderate alcohol consumption.

Action Taken or to be Taken

A Request for Applications on moderate drinking elicited a strong response and 63 applications are currently under review. Targeted research areas include coronary artery disease, hypertension, stroke, osteoporosis, breast cancer, medications interaction, behavioral issues, and the risk/benefit analysis of moderate alcohol in different populations. Research issues include: definitions of "moderate" drinking; the impact of alcohol on coronary artery disease; segments of the population most likely to benefit; the exact cellular and molecular mechanisms of these effects; and risks associated with moderate alcohol consumption. Better understanding of the precise mechanisms by which alcohol is cardio-protective could lead to pharmacologic interventions that provide the same protection without the risks that alcohol poses.

1996 Senate Appropriations Committee Report LanguageItem

Fetal Alcohol Syndrome - the Committee understands that fetal alcohol syndrome (FAS) is one of the four leading known causes of mental impairment in this country, with an estimated incidence of 1 to 3 cases per 1,000 births. FAS is fully preventable, because maternal alcohol consumption is its only known cause. The Committee strongly encourages the Institute to develop a major behavioral research initiative to achieve a significant reduction in FAS and requests the Director to inform the Committee of its plans in this area during the fiscal year 1997 budget hearings.

Action Taken or to be Taken

NIAAA remains committed to furthering the understanding of the effects of alcohol on fetuses and children. The recently completed National Academy of Sciences, Institute of Medicine study of FAS recommends NIAAA conduct studies on neurological abnormalities and other neurobiological indices to cognitive and behavioral correlates, clinical research on the adverse developmental effects of prenatal alcohol exposure, develop specific biological markers for diagnosis, and the potential role of fetal alcohol exposure in developmental disabilities. In addition, a clinical prevention trial is underway that will measure the effectiveness of reducing FAS and other alcohol-related birth defects. Health educational messages on the effects of alcohol on pregnancy will be combined with a variety of other interventions directed at women who are drinking at various levels. The message will advocate zero use of alcohol during pregnancy.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amt. Authorized	1996 Estimate	1996 Amt. Authorized	1997 Budget Estimate
Research and Investigation.....	Section 301	42§241	\$183,199,000	Indefinite	\$186,905,000
National Institute on Alcohol Abuse and Alcoholism.....	Section 464H	42§285n		Such Sums as Necessary	
National Research Service Awards.....	Section 487	42§288	5,273,000	Such Sums as Necessary	5,375,000
Total Budget Authority.....				188,472,000	192,280,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u>	<u>1/</u>
1993	n/a	n/a	180,169,000	176,619,000	2/
1994	\$173,615,000	184,700,000	184,700,000	185,617,000	
1995	3/ 182,498,000	181,328,000	181,328,000	181,256,000	4/
1996	3/ 185,712,000	188,472,000	183,733,000	188,472,000	
1997	3/ 192,280,000				

n/a = Not applicable.

- 1/ Reflects enacted supplementals, rescissions, and reappropriations. Prior to the FY 1993 Senate Allowance, NIAAA was a component of the ADAMHA appropriation.
- 2/ Excludes enacted administrative reductions of \$1,430,000, \$61,000, and \$601,000.
- 3/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.
- 4/ Excludes enacted administrative reductions of \$117,000, \$4,000, and \$68,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	9	8	8
Office of Planning and Resource Management.....	41	40	40
Office of Scientific Affairs.....	22	23	23
Office of Policy Analysis.....	4	4	4
Division of Clinical and Prevention Research.....	25	25	25
Division of Basic Research.....	14	15	15
Division of Biometry and Epidemiology	14	14	14
Division of Intramural Clinical and Biological Research.....	93	94	94
Total, NIAAA.....	222	223	223

Average GS/GM Grade

1991.....	10.4
1992.....	10.6
1993.....	10.6
1994.....	10.8
1995.....	10.8
1996.....	10.9
1997.....	10.9

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Program Administration
Detail of End-of-year Employment

	1995 Actual	1996 Estimate	1997 Request
ES-5.....	1	1	1
ES-4.....	4	4	4
ES-3.....	---	---	---
Subtotal.....	5	5	5
GS/GM-15.....	20	20	20
GS/GM-14.....	41	40	40
GS/GM-13.....	20	20	20
GS-12.....	22	21	21
GS-11.....	13	13	13
GS-10.....	1	1	1
GS-9.....	21	21	21
GS-8.....	7	7	7
GS-7.....	23	23	23
GS-6.....	6	6	6
GS-5.....	9	9	9
GS-4.....	9	9	9
GS-3.....	3	3	3
GS-2.....	---	---	---
GS-1.....	1	1	1
Subtotal.....	196	194	194
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	6	6	6
Senior Grade	7	7	7
Full Grade	2	2	2
Subtotal.....	15	15	15
Ungraded	23	18	18
Total positions, end of year.....	239	232	232
Total full-time equivalent (FTE) employment, end of year.....			
	222	223	223
Average ES level.....	4	4	4
Average ES salary.....	\$109,100	\$129,100	\$129,100
Average GS/GM grade.....	10.8	10.9	10.9
Average GS/GM salary.....	\$46,998	\$49,876	\$50,125

TUESDAY, APRIL 23, 1996.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. ANTHONY S. FAUCI, DIRECTOR

MICHAEL I. GOLDRICH, DEPUTY DIRECTOR FOR MANAGEMENT AND OPERATIONS

DR. GEORGE COUNTS, DIRECTOR, OFFICE OF RESEARCH ON MINORITY AND WOMEN'S HEALTH

DR. JOHN J. MCGOWAN, DIRECTOR, DIVISION OF EXTRAMURAL ACTIVITIES

STEVEN J. BERKOWITZ, DIRECTOR, OFFICE OF FINANCIAL MANAGEMENT AND TECHNOLOGY TRANSFER

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

Our hearings on the National Institutes of Health continue this morning with the National Institute of Allergy and Infectious Diseases. And we're pleased to welcome Dr. Anthony Fauci, the Director of the Institute.

Would you introduce the people who are with you at the table, and then proceed, Dr. Fauci.

INTRODUCTION OF WITNESSES

Dr. FAUCI. Thank you very much, Mr. Chairman.

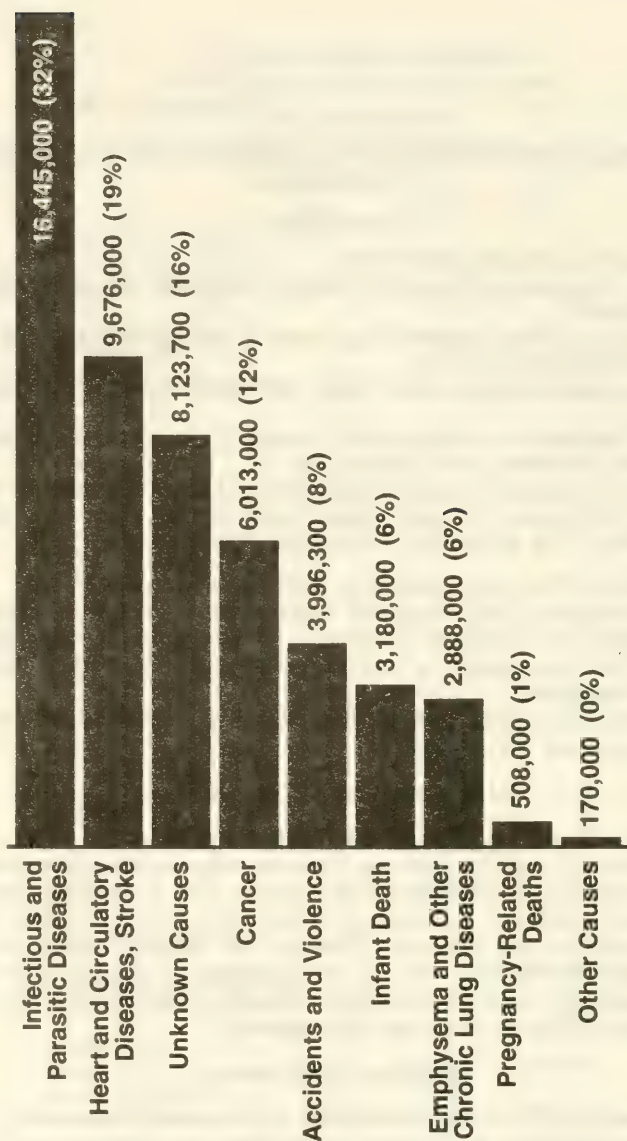
On my far left is Dr. George Counts, who is the Director of the Office of Women's and Minority Research; Dr. John McGowan, who is the Director of our Extramural Activities Program; Mr. Michael Goldrich, who is the Deputy Director for Management and Operations; Steve Berkowitz, who is the Director of the Office of Financial Management and Technology Transfer. You know Dr. Varmus and Dennis Williams from the Department.

OPENING STATEMENT

Mr. Chairman, I have submitted my written statement for the record. I would like, with your permission, to give an oral presentation of a few minutes with some graphics for you.

[The information follows:]

Worldwide Causes of Death



Source: World Health Report, 1995 (Data from 1993)

Dr. FAUCI. The mandate and the goals of NIAID are the study of infectious diseases and the immune system, the major form and the major modality of protections in the body against infections diseases. I just want to remind the committee of something that very often is not fully appreciated, that infectious diseases, in fact in 1996, are still the leading cause of death worldwide, and the third leading cause of death in the United States.

Now, the reason that this occurs is that there is a baseline steady state of infection that we're all very familiar with. But there's also the emergence and re-emergence of new infections and old infections in a different form. These are a group of headlines that encompass just 1995 and 1996. We'll get back to prior history in a moment.

[The information follows:]

The Washington Post - February 2, 1996

Drug-Resistant TB Spreads

A family of potentially-fatal drug-resistant tuberculosis has been identified in New York.

THE NEW YORK TIMES - September 23, 1995

U.S. Is Now Threatened by Epidemic of Dengue

The Hemisphere, dengue fever, a debilitating tropical disease, transmitted by mosquito, has now reached epidemic proportions in Central America and is being reported in New York.

The Washington Post - March 4, 1995

Microbe Called Threat to Drinking Water

The U.S. Environmental Protection Agency (EPA) administrator Carol M. Browner has called for a new public and private effort to improve drinking water from the source to the tap.

THE NEW YORK TIMES - May 11, 1995

Deadly Virus Is Identified in Outbreak in Zaire

Scientists have found preliminary evidence that one of the deadliest infectious agents in the world is a mysterious disease that has broken out in Zaire. The World Health Organization and the U.S. Centers for Disease Control and Prevention are working to identify the virus.

THE WASHINGTON TIMES - July 13, 1995

Tick that causes Lyme disease also carries another deadly illness

The deer tick, which causes Lyme disease, has been identified as the cause of a new bacterial illness that has killed four persons nationwide.

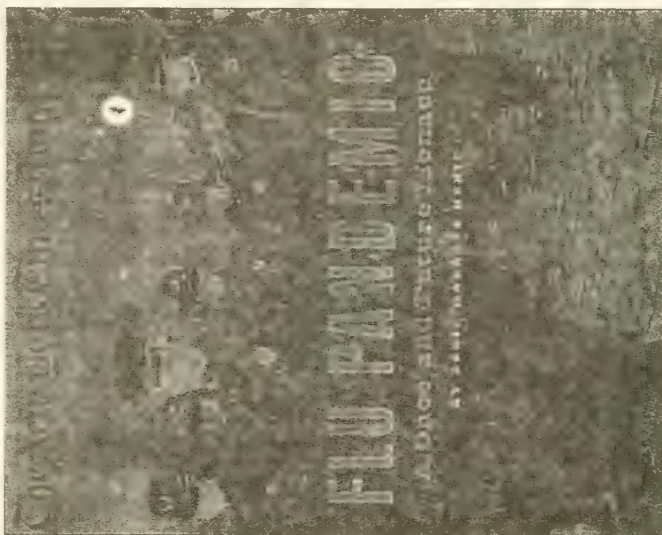
Dr. FAUCI. But as you can see, some of the things that we've had to face as a Nation and a world community over the years is the re-emergence of drug resistant tuberculosis, the epidemic of dengue, which now threatens the Caribbean and the southeast part of the United States and the terrible experience in Milwaukee with cryptosporidiosis contaminating the water supply, leaving 400,000 cases a few years ago.

Also, the outbreak of Ebola in Zaire and central sub-Saharan Africa, as well as the constant and reoccurring problem of Lyme disease, which has now emerged as the leading vector-borne causes of disease in the United States today.

[The information follows:]

Emerging Infectious Diseases: A Continuing Threat

662



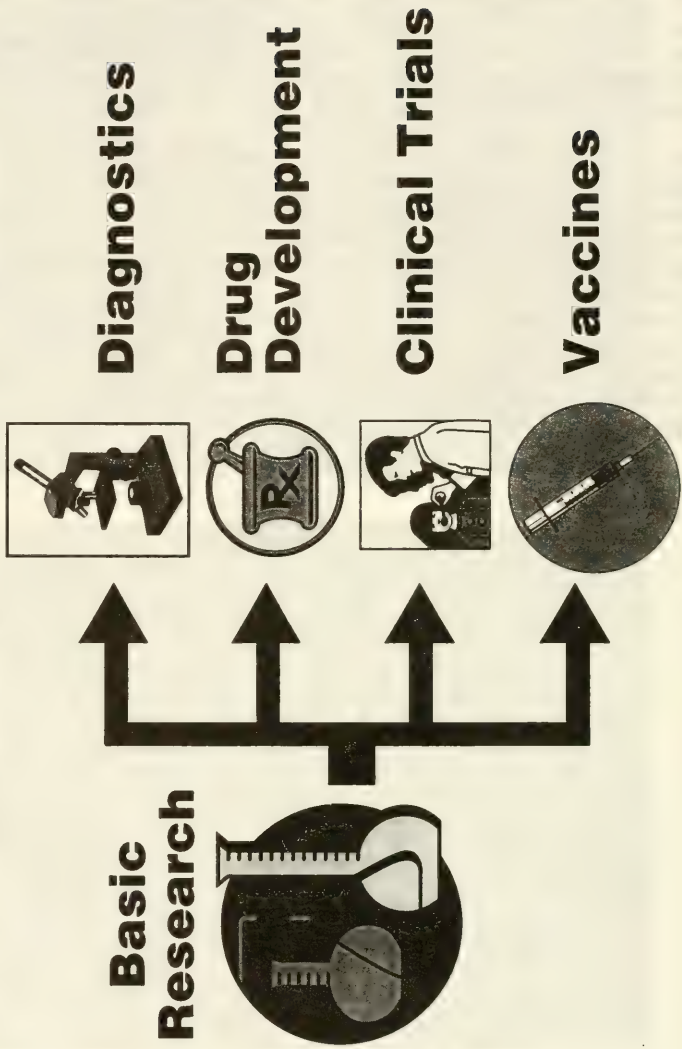
Dr. FAUCI. Now, the emergence of these are occasionally little blips on a radar screen. But we know from history that in fact these can lead to global pandemics. I show this slide, which illustrates a cover from the New York Times Magazine and one from Time Magazine, spanning a long period of time. I use this example because I discussed this actually with my father, who's 85 years old.

And in his lifetime, he's experienced two of these major global pandemics to hit mankind. One was the flu pandemic of 1918, and he was eight years old at the time. And then the AIDS epidemic, which we became aware of in the very early 1980s.

And I think it's folly for us as a Nation and as a world to think that in our adult lives, or that of our children or grandchildren, that we're not going to have the same experience that my father has experienced; to actually experience two catastrophic epidemics that have killed hundreds of millions of people, when one considers the bulk of these and the potential impact in the future.

[The information follows:]

Emerging Infectious Diseases: A Research Approach



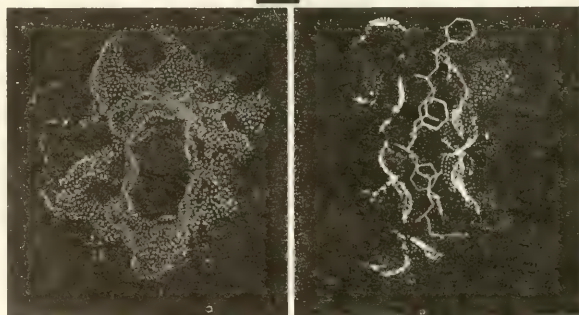
Dr. FAUCI. Now, the role of the NIH as an institution in combating these diseases is somewhat different, though complementary and synergistic with that of the CDC. As I mentioned to you and this committee before, it's a fundamental basic and clinical research approach that will identify the microorganism, lead to diagnostics, the development of drugs, clinical trials to prove that these drugs are safe and effective, and ultimately a vaccine for the prevention of these infections.

What I want to focus on is these two areas, on what we in our own society today know as the prototypic emerging new microbe. And that is the AIDS epidemic. Now, again, in several years over this period of time, I've presented to this committee some of the important findings from the initial discovery of HIV to the diagnostics to some of the early therapies. And 1995, early 1996, has been a very good year for AIDS research in the area of therapeutics.

I'd like to give you an example of something that we're proud of, because it's something that we've spoken to you a lot about in the past. And that is, the marriage of fundamental basic research with something that we can apply to the bettering of the health of our society.

[The information follows:]

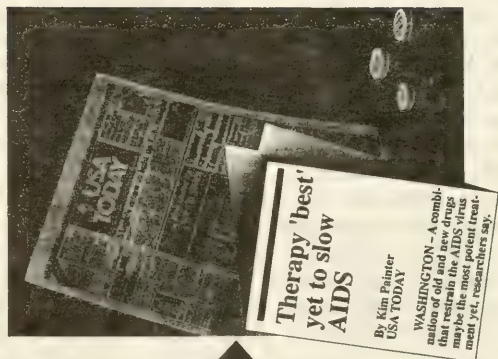
Development of Protease Inhibitors: Basic Research Leads to New Therapies



**Basic
Research**



**Clinical
Trials**



**New
Therapies**

Dr. FAUCI. And I use as one example the development and implementation of the program for the protease inhibitors used to treat HIV infection. We know a major advance has occurred in the latter part of 1995, using combinations of therapies which have clearly proven for the first time that if you treat people relatively early in the course of their disease, you can have a clinical impact, not just an impact on surrogate markers, such as CD4 counts of the virus.

Now that we have this in our armamentarium, we believe we're going to be able to push that envelope much further. The basic science that was done at the NIH led to the appreciation of the capability of targeting a particular vulnerable component of the AIDS virus in its life cycle. And this was an example, again, of collaboration between industry and the NIH, between academia and the NIH and within the NIH of multiple different institutes.

In this case, it was the Cancer Institute, NIAID and other institutes. This collaboration identified and crystallized the protease molecule and developed an inhibitor which can actually destroy the capability of this protease to continue on in the life cycle of the virus, leading to clinical trials. These clinical trials, NIH-funded, together with industry, again, is another very good collaboration between industry and the Federal Government, ultimately leading to the rapid approval now of three protease inhibitors.

And I hope next year and the year after I'll be able to report to you and this committee the clinical results of those very exciting early trials that you've read about in the paper over the past couple of years.

[The information follows:]



Dr. FAUCI. I want to turn my attention now in the final couple of minutes to the question of vaccinology. This is a picture which symbolizes the first vaccination by Edward Jenner. It is now 1996, which is the 200th anniversary, from 1796, of the first vaccination. And I think if we're to look at the advances and breakthroughs in public health, and impact on the health of the world, no one would give you an argument that vaccines and the development of vaccines to eliminate diseases such as smallpox and polio from the western hemisphere is not something that stands out clearly on top of all the things that we've been able to contribute to society.

Now, one might think that that's just something in history, because we take for granted the protection from different types of microbes. But the war against microbes essentially will never be over.

[The information follows:]

The New England Journal of Medicine



Established in 1811 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
VOLUME 334 FEBRUARY 1, 1993 NUMBER 6

Original Articles
A Controlled Trial of Two Acellular Vaccines
Against Pertussis 341
D. GRECO AND OTHERS
A Controlled Trial of a Two-Component Adju-
vanted Pertussis Vaccine 342
L. X. LI AND C. C. COVERTON

**Case Records of the
Massachusetts General Hospital**
A 40-year-old Woman with the Rapid Onset
of a Fever 342
L. X. LI AND C. C. COVERTON

Editorial
Acellular Pertussis Vaccines for Infants
and Young Children 341
K. M. EMMERT AND J. STORSAETER

**Calvin S. Seidman, M.D., and the Role of
the Journal in the Development of
Pertussis Vaccines 341**
D. J. HORTON AND OTHERS

**A Controlled Trial of Two Acellular Vaccines
Against Pertussis 341**
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vanted Pertussis Vaccine 342**
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the Journal in the Development of
Pertussis Vaccines 341**
D. J. HORTON AND OTHERS

**Benefits and Hazards of Reporting Medical
Outcomes 342**
M. R. CHAPMAN, E. L. HANSEN, AND B. A. D. BRUND

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D. GRECO AND OTHERS

January 13, 1993

JAMA

The Journal of the American Medical Association

**Decline of Childhood Haemophilus
influenzae Type b (Hib) Disease in
the Hib Vaccine Era**

**Editorial
Infections Caused by Haemophilus
influenzae Type b
The Beginning of the End?**

Dr. FAUCI. And what I want to illustrate by these two articles, one from the Journal of the American Medical Association and one from the New England Journal of Medicine, that in the past couple of years, one article was published in February 1996, was the development of a vaccine for a disease that we did not have a vaccine for: *Haemophilus influenza* type B. In collaboration with the Child Health Institute we took a disease that was the leading cause of deafness and mental retardation in children to the point of having an optimistic reason to believe that we might be able to eliminate *Haemophilus influenza* type B from our society now, purely on the basis of an effective vaccine.

You probably recall the important advance in pertussis. We had a considerable amount of difficulty with compliance of the pertussis vaccine because of the real and perceived problem with toxic side effects. This reached the point where there was poor compliance with this vaccine, particularly in certain countries like England, Sweden and Italy, where it was no longer mandated to give the pertussis vaccine, leading, unfortunately, to the re-emergence of epidemics of this terrible disease that's totally preventable.

The results from the NIH study showed that not only is the new acellular vaccine clearly more safe than the older traditional vaccine that we've used, but it's actually considerably more effective. So this was a double victory of greater safety and greater efficacy.

These are the kinds of things that we at the NIH will continue in a multi-institute collaboration to be able to add to the armamentarium of vaccines for which we do not have vaccines for, as well as improving vaccines for which we do have.

[The information follows:]

Public Health and Economic Benefits of NIH Research



- Improving health and preventing disease and premature death
- Improving quality of life and work productivity
- Expanding international competitiveness and improving global health
- Promoting technology transfer to develop vaccines, therapies, and diagnostics
- Reducing health care costs and decreasing hospitalizations

Dr. FAUCI. Finally, on this last poster, all this ultimately spelled out into real and potential public health and economic benefits of NIH research and multi-institute type research. I have given you examples of things that are relatively specific to our Institute, but you can apply this to virtually anything at NIH.

There is a booklet that we've handed out, you can look at it at your leisure. But it emphasizes some of the important contributions, ranging from improving the public health and preventing premature death to improving quality of life. An important point of expanding our international competitiveness, promoting technology transfer, and finally reducing health care costs and decreasing hospitalization.

That's my statement, and I'd be happy to answer any questions.
[The prepared statement and biography of Dr. Anthony Fauci follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) continues its long-standing commitment to basic research in immunology, microbiology and infectious diseases, those interrelated disciplines that facilitate the development of new treatments, vaccines and diagnostic tests for infectious and immunologic diseases. The Institute's sustained efforts in these fields have led to a number of recent advances that promise immediate and future benefits to the health of people in this country and around the world.

A central focus of NIAID research is the human immunodeficiency virus (HIV), the cause of AIDS. In 1995, the total number of reported cases of AIDS in this country passed the half-million mark; 62 percent of these, or more than 315,000 individuals, have died, usually in the prime of their lives. Experts estimate that AIDS will have cost the U.S. economy \$81 to \$107 billion by the year 2000.

NIAID is the lead institute for AIDS research at the National Institutes of Health and has been at the forefront of conducting and supporting a number of important research advances. Just in the past year, NIAID multidisciplinary studies have led to promising discoveries in the treatment of HIV-infected individuals, and in our search for new ways to prevent transmission of the virus.

As widely discussed in the popular press, recent studies show that potent combinations of anti-HIV drugs can significantly reduce the amount of virus in HIV-infected people as well as prolong their lives. Definitive proof of the concept of combination therapy for HIV infection came last year from studies conducted by NIAID's AIDS Clinical Trials Group (ACTG) and Terry Bein Community Programs for Clinical Research on AIDS (CPCRA), and from a large European trial.

Within the last few months, exciting new data have suggested that a new class of drugs called protease inhibitors, given in combination with other medications, may be the most powerful agents yet developed to fight HIV. Protease inhibitors work at a different stage of the HIV life cycle than do AZT and related drugs, and appear to have relatively few side effects.

NIAID-supported basic research was pivotal to the identification and characterization of the HIV protease enzyme that is blocked by these drugs, and to our understanding that interfering with this enzyme could halt HIV replication. NIAID-supported research set the stage for pharmaceutical companies to develop protease inhibitors and bring them to market. Today, NIAID is collaborating with the manufacturers of protease inhibitors to determine how best to use these drugs in combination with other medications. Clinical trials to define the optimal use of protease inhibitors are under way or imminent in the ACTG, the CPCRA, the Division of AIDS Treatment Research Initiative and the NIAID intramural research program. These efforts are excellent examples of how researchers supported by government and industry work together effectively to benefit patients.

Scientists are striving not only to suppress HIV replication and prevent opportunistic infections, but to maintain, and perhaps rebuild, the immune systems of HIV-infected individuals. NIAID intramural researchers have shown, in a randomized study, that a combination of the immune system protein interleukin-2 (IL-2) and anti-HIV drugs can significantly boost the numbers of the immune

system cells characteristically depleted in HIV-infected people. This work grew out of basic research by immunologists on the role of IL-2 in the immune system, and more than 14 years of research by NIAID researchers on the use of this substance as a possible therapy for HIV-infected individuals.

The principles established by NIAID studies of IL-2 therapy have the potential to help not only HIV-infected people, but also individuals with other diseases characterized by decreased immune system function, and perhaps those with certain kinds of cancer. In another example of the relevance of AIDS research to people with other diseases, researchers have found that the drug 3TC, developed as a treatment for HIV infection, also is effective against the hepatitis B virus.

NIAID remains strongly committed to developing a safe and effective vaccine against HIV. In February 1996, we announced a comprehensive strategy for HIV vaccine development, a plan that emphasizes the importance of both fundamental and empiric research, and joint partnerships between NIAID and industry.

A number of novel HIV vaccine approaches are in various stages of development in NIAID-supported laboratories and in the NIAID AIDS Vaccine Evaluation Group. One example is a "prime-plus-boost" protocol whereby people are first immunized with a bird virus, harmless to humans, that is genetically engineered to make HIV proteins. This inoculation is followed by a booster of either the same vaccine or the purified HIV protein.

Other methods of preventing HIV transmission also may have an important impact in curbing the epidemic. For example, NIAID-supported investigators are developing and testing topical microbicides, substances that a woman can use in her vagina before intercourse to prevent the transmission of HIV and other sexually transmitted microbes. Such interventions may be particularly important to empower women to protect themselves against HIV infection when they are unable either to avoid sex with partners who may be HIV-infected or to persuade their partners to use a condom.

In another approach, researchers have found that treating people who have other symptomatic sexually transmitted diseases (STDs) can significantly reduce the transmission of HIV. Ongoing NIAID studies will determine if treatment of an entire at-risk population, not only individuals with symptomatic STDs, may have an even greater effect.

HIV disease is the most dramatic example of an infection that has emerged to threaten human health; yet it is only one of approximately 30 newly identified diseases and syndromes recognized since 1970. Among other new threats are tick-borne diseases such as Lyme disease and ehrlichiosis, a new form of cholera, Legionnaires' disease, Ebola hemorrhagic fever, liver disease due to hepatitis C virus, the hantavirus pulmonary syndrome and toxic shock syndrome. Other diseases such as tuberculosis and certain kinds of pneumonia are increasingly problematic because of the development of resistance to antibiotics.

Infectious diseases are the leading cause of death worldwide and the third leading cause of death in the United States. In 1993, the life expectancy at birth for an American declined for the first time since 1980, due largely to deaths attributable to HIV, pneumonia and influenza. Clearly, our battle with infectious diseases must be fought on many fronts with an unwavering commitment to basic and applied biomedical research. Toward this end, the Institute has developed a comprehensive research program that will enhance our ability to detect and control infectious agents. These efforts will prepare us for unexpected infectious disease emergencies; at the same

time, we are working to reduce the burden of known diseases with new and improved treatments and vaccines.

This year marks the 200-year anniversary of a seminal event in vaccine development: the first attempts of an English country doctor, Edward Jenner, to immunize people against smallpox. Jenner's early experiments paved the way for the development of safe and effective vaccines against smallpox, and the eventual elimination of this dreaded disease. More recently, poliomyelitis has been eliminated from the Americas due to widespread immunization programs, another testament to the profound impact of safe and effective vaccines.

NIAID's vaccine research program has built on these accomplishments with pioneering research into the immune system, the interactions between microbes and the body, and new vaccine technologies. The payoff of this research has been remarkable: improved vaccines are better-tolerated and more effective than previous ones, and new vaccines exist where none were previously available. At least 14 new or improved vaccines have been licensed since 1980; the approval of several more is imminent.

The prototype of NIAID vaccine research was our international collaboration with partners in industry and academia to develop acellular pertussis (whooping cough) vaccines to improve upon currently used whole-cell vaccines. Whole-cell pertussis vaccines, although effective, are frequently associated with minor side effects that sometimes discourage parents from having their children immunized against this serious disease.

Last year, the Institute announced the results of two landmark studies that demonstrated that acellular pertussis vaccines can protect infants from pertussis with fewer side effects than the current vaccines. The availability of well-tolerated acellular pertussis vaccines promises to have a profound impact on increasing vaccine coverage, thereby preventing needless pertussis-related disease and death.

Another improved vaccine, based on technology developed by NIAID researchers, has virtually eliminated meningitis in infants due to *Hemophilus influenzae* type B (Hib) wherever the vaccine has been used. Last year, I discussed the remarkable effects of this vaccine in California; now, we have further data from the United Kingdom and elsewhere that underscore the efficacy of this vaccine. In addition to preventing the deaths of thousands of infants and sparing many others from permanent neurological damage, the Hib vaccine saves the United States approximately \$400 million in health care costs each year. Building on the precedent set with vaccines against smallpox and polio, we fully expect that widespread use of the Hib vaccine will one day eradicate Hib meningitis in this country.

Last year also saw the U.S. licensure of a highly efficacious hepatitis A vaccine, also based on the work of NIAID researchers. Worldwide, more than 1.4 million cases of hepatitis A occur each year, at an estimated annual cost of \$1.5 to \$3 billion. The new vaccine holds the promise of significantly reducing the burden of this food- and water-borne disease.

Another vaccine, developed in the NIAID Laboratory of Infectious Diseases, has been shown to be effective in preventing the severe diarrheal diseases caused by rotaviruses, which kill more than 870,000 infants and children under age 5 worldwide every year. In this country alone, annual health care costs associated with rotavirus infections are estimated at \$500 million. The new vaccine could prevent more than 1 million cases of rotaviral diarrhea and 55,000 hospitalizations of children under 5 years of age in the United States annually.

As the above examples suggest, much of our vaccine research holds promise for the most vulnerable among us: infants and children. Another serious problem in children is asthma, which afflicts 7 percent of all individuals aged 18 years and younger in the United States. As I have discussed in previous testimony, asthma-related illnesses and deaths have steadily increased in the United States in recent years, particularly in minority populations. Despite the availability of effective therapies for this disease, mortality related to asthma increased 40 percent for individuals aged 5 to 34 years between 1982 and 1991. The economic costs associated with the disease are enormous. In 1990, for example, asthma-related health care cost the country approximately \$6.2 billion; nearly half of this expenditure was for emergency room visits, hospitalizations and costs associated with death.

Over the last five years, the NIAID National Cooperative Inner-City Asthma Study has evaluated the factors involved in the increase in asthma, and designed strategies to reduce asthma morbidity and mortality. The results of this study recently became available and are quite extraordinary: 92 percent of enrolled families complied with the intervention program, which led to a striking reduction in asthma symptoms, improved quality of life and school attendance, and a 30 percent decrease in asthma-related hospitalizations. Our model of asthma intervention in the inner city, if adopted nationwide, could result in annual savings of \$300 to \$800 million by reducing emergency room visits, hospitalizations and lost school days. A continuation of the National Cooperative Inner-City Asthma Study was initiated in FY 1996 to extend and disseminate these promising results.

The last year also has led to new clues as to a possible cause of some cases of chronic fatigue syndrome (CFS), a complex condition that affects many thousands of Americans. Researchers have identified a potential link in some patients between CFS and a blood pressure regulation disorder called neurally mediated hypotension. NIAID intramural investigators and their colleagues are planning a clinical trial to see if treatment of the blood pressure disorder helps reduce CFS symptoms in those patients.

The last 12 months have been a time of optimism for the Institute, as a number of our important initiatives have come to fruition. Even more can be achieved if we continue to add to our basic knowledge of the immune system, and our understanding of different classes of organisms and how they cause disease. New and improved strategies for controlling disease--including HIV and other recent scourges--are possible with innovative research that is underpinned by a strong research base in immunology, microbiology and infectious diseases. With today's modern technologies at our disposal, and the ongoing innovations of NIAID-supported researchers, a sustained commitment to basic research will lead to new drugs, vaccines and other interventions that will benefit the health of this and future generations.

Mr. Chairman, the FY 1997 budget request for this Institute is \$584,362,000. I will be pleased to answer any questions you may have.

FAUCI, DR. ANTHONY S.

Director, National Institute of Allergy and Infectious Diseases

December 24, 1940. Brooklyn, New York

Education:

College of Holy Cross, 1962 - A.B.; Cornell University Medical College, 1966 -M.D.

Professional History:

1966-1967, Intern, Department of Medicine, New York Hospital-Cornell Medical Center. 1967-1968, Assistant Resident, Department of Medicine, The New York Hospital-Cornell Medical Center. 1968-1970, Clinical Associate, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland. 1970-1971, Senior Staff Fellow, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1971-1972, Chief Resident, Department of Medicine, New York Hospital-Cornell Medical Center; Instructor in Medicine, Cornell Medical College. 1972-1974, Senior Investigator, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1972-present, Consultant in Infectious Diseases, The National Naval Medical Center, Bethesda, Maryland. 1974-1980, Head, Clinical Physiology Section, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1977-1984, Deputy Clinical Director, NIAID, NIH, Bethesda, Maryland. 1980-present, Chief, Laboratory of Immunoregulation, NIAID, NIH, Bethesda, Maryland. 1984-1988, Clinical Professor, Department of Medicine, Division of Rheumatology, Immunology, and Allergy, Georgetown University School of Medicine, Washington, D.C. 1985-1988, Clinical Professor, George Washington University School of Medicine and Health Sciences, Washington, D.C. 1988-1994, Director, Office of AIDS Research, NIH, and Associate Director of NIH for AIDS Research, Bethesda, Maryland. 1984-present, Director, NIAID, NIH, Bethesda, Maryland.

Board Certification and Military Service:

American Board of Internal Medicine-June 21, 1972. American Board of Allergy and Immunology-March 1, 1974. American Board of Infectious Diseases-October 15, 1974. U.S. Public Health Service, July 1968-June 1970; July 1972-Present.

Professional Organizations:

American Federation for Clinical Research, American Association for the Advancement of Science, American Association of Immunologists, American Medical Association, Fellow of the American Academy of Allergy, Infectious Diseases Society of America, American Society for Clinical Investigation, Fellow of The American College of Physicians, Member, Association of American Physicians, Fellow of the Collegium Internationale Allergologicum, Charter Member of the Clinical Immunology Society, International AIDS Society, American Society for Virology, Fellow of the American Academy of Arts and Sciences, Member of the Institute of Medicine of the National Academy of Sciences (USA), Foreign Member of the Royal Danish Academy of Sciences and Letters, Member of the National Academy of Sciences (USA), Foreign Member of the Royal Academy of Medicine of Barcelona.

Offices Held:

Councillor, Eastern Section, American Federation for Clinical Research (AFCR), 1977. National Councillor, AFCR, 1978-1979. President, AFCR, 1980-1981. Recorder, Association of American Physicians, 1988-1993. Councillor, Association of American Physicians, 1993-present.

Advisory Boards and Committees:

Chairman, Allergy and Immunology Committee, MKSAP V, American College of Physicians. Advisory Panel, The American Board of Medical Laboratory Immunology. Member, Committee on Clinical Immunology and Immunopathology, American Association of Immunologists, 1980-1985. Representative of American Association of Immunologists to the Examinations Committee of the American Board of Allergy and Immunology, 1981-present. Postgraduate Education Committee, American Academy of Allergy, 1979-1982. Member, NIAID Study Group on Immunology, 1980. Member, Section of Physiology in Clinical Science of the American Physiological Society, 1980-1984. Member, Subcommittee on the Classification of Vasculitis, American Rheumatism Association 1980-present. Ad Hoc Committee, The National Foundation for Infectious Diseases, 1980-present. Subcommittee on Clinical Sciences, Publications Committee, American Physiological Society, 1980-1984. American Association of Immunologists, 1982-1985. Member, NIAID Working Group for AIDS, 1982-present. Member, American Federation for Clinical Research President's Public Policy Advisory Committee, 1983-present. Board of Directors, American Board of Allergy and Immunology, 1984-1987. Participant in the USA - People's Republic of China Immunology Cooperative Agreement, August 10-22, 1983, Beijing and Shanghai, PRC. Member, Scientific Advisory Board, Medical Biology Institute, La Jolla, CA, 1983-1984. Participant in the USA-Japan Eye Immunology Advisory Conference, November 27 to December 1, 1983, Honolulu, HI. Member, External Advisory Committee, Multipurpose Arthritis Center, Duke University Medical Center, 1984-present. Member, Honorary Advisory Board, Italian-American Medical Association, 1984-present. Member, Peripartetic Club, 1984-present. Ex Officio Member, National Diabetes Advisory Board, 1984-present. Ex Officio Member, National Digestive Diseases Advisory Board, 1984-present. Chairman, Search Committee for Director, National Institute of Child Health and Human Development, 1985. Member, Department of Health and Human Services Task Force on Alzheimer's Diseases. The Albert Lasker Medical Research Award Jury, 1985-present. Deputy Ethics Counselor, Department of Health and Human Services, 1985-present. Member, Department of Health and Human Services Committee to Coordinate Environmental and Related Programs, 1985-present. Member, Scientific Organizing Committee, Joint Meeting of the Italian Society of Immunology and Immunopathology-National Institutes of Health on "Human Lymphocyte Activation," Florence, Italy, September 5-7, 1985. Member, United States Delegation to the United States-Japan Cooperative Medical Science Committee, 1985-present. Member, U.S. Public Health Service AIDS Executive Task Force, 1985-present. Chairman, NIH AIDS Executive Task Force, 1985-present. Coordinator, NIH AIDS Research, 1985-present. Member, Scientific Seminar Subcommittee, National Institutes of Health Centennial Program, 1985-1987. Member, Advisory Board, Clinical Immunology Newsletter, 1986-1988. Member, Scientific Organizing Committee, International Conference on Lymphocyte Activation and Immune Regulation, Newport Beach, CA, February 28-March 2, 1986. Member, Planning Committee, Clinical Immunology Society, 1986. Member, International Advisory Committee, International Conference on AIDS, Paris, France, June 23-25, 1986. Member, Advisory Group, Institut Scientifique Roussel-Uclaf, 1987-1989. Ex Officio Member, National Kidney and Urologic Diseases Advisory Board, 1987-present. Member, International Programme Committee, 8th International Congress of Immunology, Budapest, Hungary, 1987. Member, International Advisory Committee, IVth International Conference on AIDS, Stockholm, Sweden, June 12-16, 1988. Member, NIH Resource Allocation Group, 1987-1989. Member, Committee for the Coordination of Research Programs on the Acquired Immunodeficiency Syndrome of the Ministry of Health of Italy, 1988-present. Institute of Medicine Roundtable for the Development of Drugs and Vaccines Against AIDS, 1989-1994. Member, International Program Committee, Vth International Conference on AIDS, San Francisco, California, 1990. Member, Governing Council, International AIDS Society, 1990-present. Member, Selection Committee for the National Public Service Awards, 1990. Member, Scientific Review Committee, VII International Conference on AIDS, Florence, Italy, June 16-21, 1991. Member, Scientific Program Committee, VIII International Conference on AIDS, Amsterdam, The Netherlands, July 19-24, 1992. Member, International Programme Committee, IX International Conference on AIDS, Berlin, Germany, June 6-11, 1993. Member, International Steering Committee, Tenth International Conference on AIDS, Yokohama, Japan, August 7-12, 1994.

Editorial Boards:

Dr. Fauci has been or is on the Editorial Board of 28 scientific journals in the field of immunology, allergy and infectious diseases. These include: The Journal of Clinical Investigation, The Journal of Immunology, Journal of Infectious Diseases, Journal of Clinical Immunology, The Journal of Experimental Medicine, The New England Journal of Medicine. Dr. Fauci is also the Editor of one of the major textbooks of medicine in the world, "Harrison's Principles of Internal Medicine."

Awards and Honors:

Alpha Omega Alpha. Kileen Prize for Excellence in Chemistry (College of the Holy Cross). John Metcalfe Polk Prize for General Efficiency (Cornell University Medical College). Alfred Mortitz Michaelis Prize for Efficiency in General Medicine (Cornell University Medical College). U.S. Public Health Service Meritorious Service Award, 1979. Arthur S. Flemming Award, 1979 - Given to the 10 outstanding employees in the U.S. Federal Government. Squibb Award of the Infectious Diseases Society of America, 1983. U.S. Public Health Service Distinguished Service Medal, 1984. Food and Drug Administration Commissioner's Special Citation, 1984. 1985 Citation Classics (Current Contents) for article - A.S. Fauci, D.C. Dale, and J.E. Balow: Glucocorticosteroid therapy: mechanisms of action and clinical considerations. *Ann. Intern. Med.* 84: 304-315, 1976. Who's Who in America, 44th Edition. Who's Who in Science and Technology, 2nd Edition. 1985 Stanford University Center Survey of the American Rheumatism Association membership ranked the work of Dr. Anthony S. Fauci on the treatment of polyarteritis nodosa and Wegener's granulomatosis as one of the most important advances in patient management in rheumatology over the past 20 years. The Clemens von Pirquet Award of Georgetown University Medical Center, 1986. Doctor of Science, Honoris Causa, College of the Holy Cross, Worcester, MA May 29, 1987. The Kober Lecture Award of the Association of American Physicians, 1988. Public Health Leader of the Year Award of the Commissioned Officers Association of the U.S. Public Health Service, 1988. The National Institutes of Health Clinical Center Annual Distinguished Clinical Educator Award, 1988. 1988 Citation Classics (Current Contents) for article - A. S. Fauci, B. F. Haynes, P. Katz: The spectrum of vasculitis. *Ann. Intern. Med.* 89: 660-676, 1978. The Leadership Award of the Columbus Citizens Foundation, Inc., for "Inspired Leadership and Outstanding Achievement in the Field of Medical Research," New York, NY October 8, 1988. American Association for the Advancement of Science/Westinghouse Award for Public Understanding of Science and Technology, 1988. The National Hemophilia Foundation Special Award for Research in AIDS, 1989. The Lee P. Brown National Public Service Award of 1989 presented by the National Academy of Public Administration and the National Society for Public Administration. The Duke University Award for Rheumatologic and Immunologic Research, 1989. The William Beaumont Award of the American Medical Association, 1989. The academic Excellence Award from Children's Hospital National Medical Center, Washington, DC, 1989. The Surgeon General's Exemplary Service Medal, 1989. The Surgeon General's Medallion, 1989. The 1989 Achievement Award of the American Association of Physicians for Human Rights. The 1989 National Medical Research Award of the National Health Council. The Flame of Hope Award of the Terri Gotthelf Lupus Research Institute, November 2, 1989. The 1989 Maxwell Finland Award in Infectious Disease presented by the National Foundation for Infectious Diseases. The 1989 Helen Hayes Award for Medical Research. The Excellence in Public Service Award of the Committee for the Support of Public Service, May 9, 1990. The 1990 Lifetime Science Award of the Institute for Advanced Studies in Immunology and Aging, Washington, DC. Doctor of Science, Honoris Causa, Mount Sinai School of Medicine, New York, NY, May 18, 1990. Doctor of Science, Honoris Causa, Neumann College, Aston, PA, May 19, 1990. Doctor of Science, Honoris Causa, Georgetown University School of Medicine, Washington, DC, May 26, 1990. Doctor of Science, Honoris Causa, Hahnemann University Graduate School and School of Medicine, Philadelphia, PA, June 1, 1990. 1990 Science Citation Index ranked Dr. Fauci as the eighth most-cited scientist among 1.3 million scientists publishing in the time period 1981-1988. 1990 Humanitarian Award of the Human Rights Campaign Fund Federal Club of Houston. The First International Chiron Prize for Biomedical Research awarded by the Scuola Superiore di Oncologia e Scienze B Biomediche (Genoa) and the Scuola Internazionale di Oncologia e Medicina Sperimentale (Rome), 1990. Doctor of Medicine and Surgery, Honoris Causa, Università di Roma, "La Sapienza," Rome, Italy, 1990. The Fifth Annual Gene Frey Memorial Award for Medicine, The Whitman-Walker Clinic, Washington, DC, November 17, 1990. The 1990 Presidential Award of the New York Academy of Sciences. Fellow, American Academy of Arts and Sciences, 1991. Doctor of Science, Honoris Causa, St. John's University, Jamaica, NY, May 19, 1991. Honorary Fellowship, The New York Academy of Medicine, March 20,

1991. The Award of Courage from the American Foundation for AIDS Research for "extraordinary leadership and personal scientific contributions to AIDS research," December 2, 1991. 1991 Institute for Scientific Information Database Analysis indicated that of the more than 1 million scientists in the world who published in the decade 1981-1990, Dr. Fauci was the 2nd most cited (*Nature* 355: 101, 1992). Foreign Member, Royal Danish Academy of Sciences and Letters, 1992. Elected to the National Academy of Sciences (USA), 1992. 1992 Sidewalks of New York Science Award from the Big Brothers/Big Sisters of New York City, Inc., New York, May 5, 1992. Establishment of the Anthony S. Fauci, M.D. Perpetual Scholarship by the Sons of Italy Foundation, May 14, 1992. The Cornell University Medical College Alumni Award of Distinction, May 27, 1992. Doctor of Science, Honoris Causa, Long Island University - Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Brooklyn, NY, June 7, 1992. Honorary title of "Il Commendatore della Repubblica" conferred by the President of the Republic of Italy (awarded 22 June, 1988 in Rome and presented 2 June, 1992 by the Italian Ambassador to the USA in Washington, DC). Election to Fellow, American Association for the Advancement of Science. The Thomas H. Ham - Louis R. Wasserman Award of the American Society of Hematology, December 1992. The Department of Health and Human Services Secretary's Certificate of Appreciation for "Outstanding contribution in the implementation of the parallel track initiative of the U.S. Department of Health and Human Services," January 6, 1993. The 1992 Dr. Nathan Davis Award for Outstanding Public Service. Awarded by the American Medical Association to a "Member of the Executive Branch of the Federal Government in Career Public Service." Visiting Professor of Medicine at a large number of major medical schools throughout the country. The Department of Health and Human Services Secretary's Certificate of Appreciation for "Outstanding contribution in the implementation of the parallel track initiative of the U.S. Department of Health and Human Services," January 6, 1993. The 1992 Dr. Nathan Davis Award for Outstanding Public Service. Awarded by the American Medical Association to a "Member of the Executive Branch of the Federal Government in Career Public Service." The Howard University Outstanding Achievement Award, 1993. 1993 Citation Classics (Current Contents) for article - H. C. Lane, H. Masur, L. Edgar, G. Whalen, A. H. Rook, and A. S. Fauci: Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N. Engl. J. Med.* 309: 453-458, 1983. Doctor of Science, Honoris Causa, Medical College of Wisconsin, Milwaukee, WI, May 15, 1993. The R. E. Dyer Lectureship Award, National Institutes of Health, May 19, 1993. Doctor of Science, Honoris Causa, Bard College, May 29, 1993. Doctor of Science, Honoris Causa, Bates College, May 31, 1993. The Humanitarian Award of the Tiro a Segno Foundation, 1993. The Cartwright Prize of Columbia University College of Physicians and Surgeons, New York, NY, November 29, 1993. Doctor of Science, Honoris Causa, State University of New York at Farmingdale, May 19, 1994. Commission of Honor Award, State University of New York at Farmingdale, May 19, 1994. Doctor of Science, Honoris Causa, The University of Connecticut Health Center, Farmington, CT, May 16, 1994. The National Italian American Foundation Award for Special Achievement in Medicine and Science, October 29, 1994. Honorary Fellowship Award, American Academy of Allergy and Immunology, 1995. The Thirty-Eighth Theobald Smith Award of the Albany Medical College, 1995. The Ernst Jung Prize for Medicine, Hamburg, Germany, 1995. The Ellis Island Medal of Honor for Medical Research, 1995. Gold Medal of the Autonomous University of Barcelona, Spain, 1995. Membership in the Royal Academy of Medicine of Barcelona, 1995. Internist of the Year Award of the Catalan Society of Internal Medicine, 1995. The Institute for Scientific Information ranked Dr. Fauci as the fifth most cited scientist in the world over a period 1981-1994 (*The Scientist*, October 2, 1995). Doctor of Science, Honoris Causa, Duke University, May 14, 1995. The Steven C. Beering Award of Indiana University School of Medicine, November 1995. The Lilly Award Lectureship, November 1995.

Publications:

Dr. Fauci has authored over 850 scientific publications in the field of basic and clinical immunology and infectious diseases.

EMERGING DISEASES

Mr. PORTER. I've asked you this before, and this goes directly along the lines of what you were just talking about. But you said the war against microbes will essentially never be over, which means to me that the ability for mutations for bacteria and viruses is always there, and the question is, how rapidly are we gaining on this? And are we winning the war, essentially, or losing it? Or are we just holding our own?

And we read, for example, about bacteria that become resistant to antibiotics and we have to look for new ways of combatting bacteria that we thought at one time were controllable. Can you speak further on that?

Dr. FAUCI. Sure. That's an excellent question. I think one has to almost look at this philosophically. The purpose of these microorganisms is to survive. They will do, and they have the genetic capability, of doing whatever it is to survive; the same thing as the survival of our species.

I do not think that it is possible to win the war completely in the sense of eliminating microbes that will be disease threats to humans. But if you ask the question, as you did, are we holding our own or doing better, I would evaluate it, Mr. Chairman, as we are holding our own and then some. And when I say, and then some, I mean that every once in a while, we get an advance, such as the elimination of *Haemophilus influenza* type B, or the elimination of polio.

That's generally balanced by an emerging microbe, such as the hantavirus or the Ebola virus. Most of the time, those are not broad public health threats. But every once in a while, you get something like HIV or a flu pandemic that is a public health threat. You also have the ever-present threat of the development of microbial resistant microorganisms, because of the use of antibiotics.

Now, underlying all of this statement is the fact that we clearly will lose the war as it were, if we assume that we have now reached a state of comfort vis-a-vis the microorganisms; that we don't have to continually invest, as we have, with the help of this committee, in biomedical research at its very basic form, in microbiology and in immunology.

But the answer to your question is, we're at least holding our own. But we have to be continually vigilant from the standpoint of research, whereas surveillance, as I mentioned, is something that is fundamentally more of the Centers for Disease Control and Prevention.

INFECTIOUS DISEASES

Mr. PORTER. The statistics that you just presented, Dr. Fauci, on causes of death, were causes of death worldwide, correct?

I guess my first question would be, are infectious diseases the leading causes of death in the United States as well?

Dr. FAUCI. No. It's the third leading cause of death in the United States. In fact, that has escalated from the fifth or so over the past several years, for a combination of reasons. One is obviously the

AIDS epidemic beginning in the early to mid-1980s, and is a reason for the boost from several places down in the ladder up to third.

Other reasons are deaths in hospitals due to drug-resistant microorganisms and deaths due to pneumonia that have now become resistant to microorganisms. So if you were to say, what are the two major things, it's the emergence of a new disease as an epidemic, as well as the emergence of drug-resistant microorganisms. So it is third in the United States.

AIDS RESEARCH

Mr. PORTER. And how has AIDS affected the worldwide figures? In other words, have infectious diseases always been the leading cause of death worldwide, or has AIDS pushed that to the top?

Dr. FAUCI. AIDS has made it a comfortable margin now. Generally, it has been a race between infectious disease and nutrition and other types of generally preventable phenomenon. Right now, with the AIDS epidemic, and the projections that by the year 2000 there will be between 40 and 100 million HIV infected individuals worldwide, I think that margin that I showed you on the graph will probably extend even further in relative percentage.

ANTIMICROBIAL AGENTS

Mr. PORTER. Because I'm certain that my colleague, Nancy Pelosi, is going to ask you about AIDS matters, I'm going to try to cover some other ground.

Last September, a conference unveiled information about a new crop of antibiotics being developed that may overcome the resistance problems with the antibiotics currently on the market. I know there has been great concern that we will run out of effective antibiotics for some diseases before new drugs are developed which don't have resistance problems. Do the new drugs reported last September represent an earlier than expected breakthrough?

Dr. FAUCI. Again, I hesitate to use the word breakthroughs under circumstances such as this, Mr. Chairman. But I believe it's an important advance; at least it's a rekindling of interest and awareness of the seriousness of the problem. The conference you're referring to was what we call the ICAC conference on antimicrobial agents that was held in San Francisco last fall. And what was revealed at that meeting was new data, particularly on some new drugs that will combat the difficulty that we're facing with resistance of drugs like staphylococcus, as well as pneumococcus.

We really are developing a significant problem in that there are some drugs, such as vancomycin, which are the last fortress that we have against some of these microbes. And we're starting to see the emergence of microbes that are resistant to even those last ditch, very important drugs. But the conference revealed a variety of new classes of antimicrobials. I could go through them, but they have very strange sounding names. But there's at least a dozen of them, including the new betalactams against the staphylococci.

So although I don't think we can claim victory, and I don't think we should call it a breakthrough, I feel much more confident now than I did a few years ago in that we're starting to have the development of new drugs. These drugs not just a replacement for something that's already on the shelf, but gives you value added with

regard to resistance. And I hope we continue that trend. We certainly are supporting that at the NIH.

Mr. PORTER. Are these drugs on the market yet?

Dr. FAUCI. Some of them are.

Mr. PORTER. Some of them are?

Dr. FAUCI. Some of them are, yes. In fact, virtually all of them have corporate sponsors. An example is one of the betalactams Bristol Meyers Squibb is developing. A drug called the glycolglicines is at Wyatt Earst and others. So we have interest on the part of the drug companies, which I think is very important, for obvious reasons.

TUBERCULOSIS

Mr. PORTER. Science Magazine reported in January that a modified microbe may lead to a more effective tuberculosis vaccine. Does this have any impact on the population currently infected, and could this vaccine protect against the drug-resistant forms of TB?

Dr. FAUCI. The answer is, for people who are already infected, a vaccine of that sort would not have impact on those individuals. The host offenses of individuals who are already infected would be important in blocking what we call the activation of tuberculosis. So in that sense, it wouldn't have an impact on the population currently infected.

Clearly, individuals who are not exposed or have not been infected would have great benefit from a new vaccine such as this sort.

Mr. PORTER. What progress is being made in developing faster diagnostic tests for TB? Is there substantial private sector investment in TB tests because of their potential commercial value?

Dr. FAUCI. Well, we have created an Action Plan with the boost that we had in TB research a few years ago, when we became aware of the emergence of multiple drug resistant tuberculosis. We feel very good about this. We really had an infusion of money that we redirected which was given to us from the Director's office, and then new money was appropriated that allowed for a full court press, in diagnostics, therapeutics and vaccine research.

With regard to the diagnostics that you've mentioned, there is a very rapid tool now which makes use of a molecular mechanism. It's a phage of a virus that infects TB that has a gene for an enzyme called luciferase, that is able when it gets catalyzed to be active, creates in the culture medium a light spot that you can see.

So something that would take weeks to determine, a, if you have TB, and, b, if it's drug-resistant, you can now determine in a very relatively short period of time. I think that's a major boost towards diagnosis. Because if you have to wait around for cultures, sometimes, particularly when you have the rapidly fulminant type of disease, you can lose the patient while you're trying to determine if you have the microbe and/or a drug-resistant microbe. So that's been a very important advance in diagnostics.

CHRONIC FATIGUE SYNDROME

Mr. PORTER. My last question before I call on Ms. Pelosi, could you give us an overview of where we are on chronic fatigue syn-

drome? I understand that there is, and your testimony mentioned, a possible link between CFIDS and a blood pressure disorder.

Dr. FAUCI. Right.

Mr. PORTER. Could you give us an overview of where we are?

Dr. FAUCI. As you know, and as I've reported to this committee several times in the past, we have a number of approaches toward chronic fatigue syndrome. We obviously need to clarify this very puzzling but I believe quite real disease. One of the observations that was made is that there is evidence that there is what we call neurally mediated hypotension, or the instability of blood pressure that is generally regulated by the nervous system.

And that is now being looked at to determine if indeed this is the case. And there is some evidence to indicate that at least in a subset of chronic fatigue syndrome patients, that is the case. There are now studies going on, collaborations up at Johns Hopkins and other institutions, with the NIH, in looking at the salt intake or giving a hormone, such as one of the cortisone derivatives, that would allow one to have a greater equanimity or equilibration. So I think this is an important lead.

Mr. PORTER. Anything else going on in this area?

Dr. FAUCI. First of all, I'm sure you've heard about the questions of, is this an infectious disease. And we have grants that are clearly looking, with very sensitive microbial probes, as to whether or not there is in fact a microbe that's common to chronic fatigue sufferers. And the answer to that is, there is not at this point, even though we're trying very hard to determine if there is. So that's another example.

Also, we're looking for investigating in a more detailed fashion the existence of this syndrome in adolescents and children. We have a workshop coming up in several months in which we're going to try and put all our heads together to see if we can get a better handle on the chronic fatigue syndrome in younger individuals.

Mr. PORTER. Ms. Pelosi.

Ms. PELOSI. Thank you very much, Mr. Chairman.

I want to just follow up, to make sure I understood clearly what Dr. Fauci said about chronic fatigue syndrome. There is therefore no scientific evidence to support a finding that chronic fatigue syndrome is caused by an infectious disease?

Dr. FAUCI. That is correct.

Let me just add something to that, Ms. Pelosi, that's important. There is a syndrome that I believe would constitute a subset of chronic fatigue syndrome, what we call post-viral asthenia. That is a very real syndrome of when you get a serious infection, sometimes a serious influenzae infection, that you could go weeks or months feeling weak and fatigued. That's a real phenomenon.

Now, the question that you asked me, is there a common denominator microbe that there's any evidence is causing chronic fatigue syndrome, and the answer to that is definitely no. But I wouldn't want to then let fall out the possibility, which is real, that there are individuals who do have a post-viral syndrome that can go on for months and be just like chronic fatigue syndrome, and in fact might be a subset of chronic fatigue syndrome.

Ms. PELOSI. Are you pursuing it?

Dr. FAUCI. Definitely, yes.

HIV AND AIDS RESEARCH

Ms. PELOSI. Dr. Fauci, as always, it's a pleasure to welcome you here, particularly this year, to thank you for all that you do, and the good news that you have had on the combination therapies and the protease inhibitors that give us some hope that this investment has some new payoffs. I know that it would and has. But it does raise some questions, would we call them breakthroughs, in this case?

Dr. FAUCI. I hate to use that word.

Ms. PELOSI. I know you do.

Dr. FAUCI. Why don't we say advances.

Ms. PELOSI. Advances, I'll scratch breakthrough, make that advances, in AIDS treatment in the last year. Could you tell us something more about the effectiveness of these therapies, these treatments, compared to what was available only one year ago when you were here?

Dr. FAUCI. I think I can explain clearly just using two examples. Monotherapy for HIV is what we had available to us in years past and, it's very clear that if you ask a drug like AZT alone to help someone who has advanced disease, you will see a benefit. But it will be a short lived benefit for a number of reasons, probably the most important of which is the developing emergence of resistance to AZT. So there is benefit, but it's not good enough.

And I've said this before to this committee several times. The two important things that have happened over the past year is one, the concept of combination therapy being better than monotherapy. But even more important, when given to individuals relatively early in the course of their disease, when their CD4 count is between 350 and 500 and they are without symptoms, that for the first time ever, when you compare AZT alone with AZT plus DDC or AZT plus DDI, you have an effect not only on the CD4 count and the viral level, but you actually have a decrease in mortality in those individuals as well as a decrease in incidence of AIDS defining illnesses.

That's something that really is not fully appreciated. That's the first time that that's ever been shown. We've had a lot of surrogate marker type stuff with AZT.

Now, superimposed upon that, which is really exciting me, I wouldn't call it a breakthrough, but it's certainly making me excited—

Ms. PELOSI. God knows what a breakthrough is, what you will do then.

Dr. FAUCI. I will let you know. [Laughter.]

But the thing that's happened, literally in parallel with that, is the demonstration that the protease inhibitors, particularly when given in combination, and again, this is something that, in people who are relatively advanced in their disease, in greater than 85 percent of individuals, brought the virus down to below detectable levels in the blood. And when I say below detectable levels, I mean by very sensitive PCR assay, which would be a few hundred copies of the virus per ML of plasma, below detectable level for up to 40 weeks.

Now, there are a lot of questions and caveats about that. And that's going to be how long does that last, and when you decide to give the drug earlier in combination, will the cumulative toxic side effects outweigh the ultimate clinical benefit, and also, would you develop resistance.

But just the very fact that we have an armamentarium now of a combination that we know will give you a greater clinical benefit, and one of the drugs in that combination is by far the most powerful anti-retroviral agents that we've had experience with so far, makes me very anxious in positive anticipation of the clinical trials that are going to give us the answer to what the ultimate clinical benefit is going to be. And that's one of the things that I'm going to relish, hopefully, coming before this committee in a year or two or three or whatever, to give you those results.

Ms. PELOSI. I can't wait until next year.

In light of all of this, Dr. Fauci, this therapy is more expensive than what we have——

Dr. FAUCI. Yes.

Ms. PELOSI [continuing]. In order to provide it. And we're pleased that our Chairman very generously provided the leadership to put funds into the appropriations bill for this year, and the Administration has a similar amount for the 1997 budget. I would hope that it would be double, because for this year, we're only talking half a year. But I am satisfied by the Secretary's answer that we'll revisit the issue as we go along. That was my view of what she said, anyway, that was my optimistic view, listening to what she had said.

What is being done by your Institute and other Federal agencies to develop a revised standard of care for treating HIV infection, and what needs to be done to get the word out to practicing physicians?

Dr. FAUCI. We have a system in place where one can call and get the very latest information on clinical trials that has been in use now for several years. Our 1-800-TRIALS-AIDS number allows a person to call up in Spanish or English and find out exactly what the latest results are.

But even more importantly than that, we are going to be collaborating with other agencies in a state of the art conference. We're going to probably have a double, two-layered approach where we'll first bring investigators together to establish the state of the science about what we really know about these agents, and then involving multiple agencies come out with some state of the art consensus conference type recommendations.

Ms. PELOSI. What timetable do you have on that?

Dr. FAUCI. Well, we probably won't have the consensus conference type of an approach until the fall. In the spring we're going to be evaluating all of the scientific data. But I don't think we'll be able to make the kinds of recommendations that would have the impact on the multiple different agencies. I think we'd have to wait. And it's scheduled for some time in the fall.

Ms. PELOSI. There's a great deal of interest, as you know, from the highest levels in the research community and our community, and the delivery of care, across the board to the grass roots level

in the revised standard of care. Because we just have to have this information available.

Dr. FAUCI. There's also a lot of individual things. I was on the beta program out of San Francisco of a group that I'm sure you're familiar with that broadcasts in California. And I was on for an hour going over the state of the art, which was very widely broadcast.

We'll be doing unofficial outreach until we get an official, state of the art type recommendation. So we're not going to let it wait and say nothing until then.

TOPICAL MICROBICIDES

Ms. PELOSI. Thank you, Dr. Fauci.

The last few. What advances have been made in research on blocking HIV transmission to women through topical microbicides?

Dr. FAUCI. Yes. The topical microbicide initiative, as you know, has been given a very high priority from the Secretary's level down. We now have the three-pronged approach: the development, the clinical trials and the ultimate implementation of that. And what we have done is have a number of industrial partners that we have been working with in a consortia to develop new agents and to begin clinical trials with them. In fact, we had a meeting with several of them that reached the level of the Vice President.

When President Clinton, at the AIDS summit in December, asked Vice President Gore to put together a group of government and industrial individuals to meet and talk about how we could help each other, how industry can help government and how government can help industry, very, very clearly visible in that group were the groups who were involved in the topical microbicides. So that did not fall between the cracks in our dealings in that level.

LEVINE COMMISSION

Ms. PELOSI. As you know, there's a great deal of interest here on Capitol Hill, too. And our colleague, Congresswoman Morella, has been very interested in this.

Ultimately, hope for women worldwide on this issue rests with the development of safe and effective HIV vaccine. As you know, the Levine Commission recently recommended establishing a restructured trans-NIH vaccine research effort. What is NIH doing to respond to these recommendations?

Dr. FAUCI. We have already met at least a couple of times with Dr. Varmus, Dr. Paul and the other institute directors, of how we are going to implement each of the major 14 points in the large overview. And then after we do that, we'll go into this particular subgroup. So we are already in the process of examining how we'll be able to implement the recommendations.

I might mention that the main thrust of the Levine recommendation to give greater emphasis to vaccines and to make it a high priority, is something I share very strongly in. In fact, we put together last year something that we have available for you: Strategy and Opportunity for HIV Vaccine Development, which is the statement, very, very briefly, which emphasizes the need for marrying basic and empiric research; the need to establish in good faith partnerships with industry.

Because we can't do it without industry, in order to delineate before hand the kinds of conditions and criteria that the collaboration will exist upon. And that has met with very favorable reviews from our industrial partners, which I'm very encouraged by, because there was a bit of a discouraging air about getting involved in vaccines, as well as blueprints for getting the community involved at the very grass roots, the people who will be the subjects of the vaccine study.

So we're very enthusiastic about continuing and accelerating our vaccine effort, as per the recommendation of the committee.

Ms. PELOSI. My time is up, I just want to make sure I understand. So now, at NIH, the NIAID will be involved in product development in terms of vaccine?

Dr. FAUCI. In consortia with the companies.

Ms. PELOSI. I'll have more questions, but hopefully the Chairman will give us another round.

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Miller.

Mr. MILLER. I apologize for missing your presentation. Dr. Paul was in my office, and then I ran over. So you can blame Dr. Paul. [Laughter.]

PROTEASE

No, I got tied up on a phone call. I apologize for that. But I read some of your comments. And I'm going to follow up on some of the things that Ms. Pelosi was asking. You only like to use the word "advance" but this protease, is that considered a jump?

Dr. FAUCI. Yes. That's a big advance. The reason——

[Laughter.]

Let me explain——

Mr. MILLER. What would be the next step? Other than an advance, what would you call it?

Dr. FAUCI. The reason I don't use the word breakthrough, it's not because of the present company, because whenever you use the word breakthrough, the press generally distorts it out of proportion. And then you wind up having a discouraged and disillusioned public, when everyone gets enthusiastic about something, they call it a breakthrough. And if it doesn't turn out that it really works ultimately for the good, for the clinical improvement, your credibility as a scientist and a science administrator is lessened.

For example, when people called AZT a major breakthrough, and it turns out that for the long term benefit of individuals, it was not what people expected it to be. So I don't mean to be facetious about it, but I really hesitate to use it. But as I mentioned to Ms. Pelosi, I consider the protease work, the data, and the results, to be a very important advance in HIV therapeutics.

Mr. MILLER. How long have they been testing protease?

Dr. FAUCI. For a few years now. It's really one of the more rapid evolutions. I mentioned that in my opening statement, protease was a great example of the transition of fundamental basic science into the development of a product, a clinical trial and then the FDA approval of a drug. It really was, I think it's going to go down as a textbook example of that.

People at the NIH, in industry, and our academic colleagues that we support, were looking at the specific function of the genes of HIV. And one of the approaches of that was to isolate that and crystallize them. Once the protease is crystallized, which is a very important enzyme that the virus needs in the latter part of its life cycle, once that has occurred, it is relatively easy to tailormake a compound that could disrupt the capability of that enzyme to be able to perform its function.

This crystallization happened with a collaboration that took place between industry and the NIH. And then after that, a drug was developed, clinical trials were started, they took a period of a few years to come to fruition. They were reported at scientific meetings at the end of the 1995 calendar year. And at the beginning of 1996, three of the drugs were approved by the FDA. And that was, again, from basic science right up through approval of the drugs. That was very rapid.

Mr. MILLER. Is it a first generation protease, or is it another whole area we're going to be getting into?

Dr. FAUCI. This is an entirely new class of compounds. That's a very good question. When AZT came, DDI, DDC, D4T, 3TC were all different generations of the same drug, which is a reverse transcriptase inhibitor. This was a new class of compounds that were used.

Mr. MILLER. And so this would be considered a first generation?

Dr. FAUCI. First generation, yes.

Mr. MILLER. And there's likely going to be more?

Dr. FAUCI. Yes, exactly.

INDUSTRY COLLABORATION

Mr. MILLER. Okay. As Ms. Pelosi was asking on the role of the private versus the public, could you tell us more? There's a tremendous amount going on, obviously, in the private sector. But are there problems with the competition to get the patents and the sharing of information in that area?

Dr. FAUCI. There will always be competition. That's one of the things that drives industry. And I think it's a healthy force. The difficulty is if it becomes so secretive that it inhibits the advance of scientific knowledge.

What I was very encouraged by last year and the year before, is the companies got together on their own, and we were very pleased with that. It was led by Merck and others who got together and decided that they, in an unprecedented way, were going to share information, particularly information out of phase one. What we mean by that is if a company or group of companies are trying to develop a concept of a new drug, they would generally keep their data totally to themselves and not share it, unlike people who are in academic, where you would report something and the literature would become public knowledge. They would generally not make that public knowledge.

They agreed that in order to obviate this duplication that might occur of one company going down the same wrong track that another company went, that they would actually share data. It's really worked very, very well. I think that that intercompany collaboration is a very good example of the kinds of evolving that we're see-

ing of openness, when you're faced with a catastrophic epidemic like this.

And our approach towards vaccine, that I mentioned to Ms. Pelosi, about sitting down the NIH as an institution, with the companies and dealing with them in a good faith partnership, and not taking the approach which they get very nervous about, that, trust us, work with us, and we'll let you know later on whether we're going to fulfill the partnership, we now have firm commitments with them. I think those two things are bringing us further ahead than we were a few years ago.

Mr. MILLER. How do the antitrust laws fit into this?

Dr. FAUCI. Well, I can tell you, speaking to the CEOs of all those companies, their lawyers dissected that out real carefully before they developed that inter-company collaboration. And it does not violate any of the antitrust laws.

Mr. MILLER. It's not causing any problem?

Dr. FAUCI. No.

Mr. MILLER. Is it causing any problem in any other areas at all? I'm not a lawyer, so I don't know.

Dr. FAUCI. No, it doesn't seem to be.

INTERLEUKIN-2

Mr. MILLER. You were doing work on something called IL-2. You mentioned this in your report.

Dr. FAUCI. Yes, interleukin-2.

Mr. MILLER. That's different from protease?

Dr. FAUCI. Yes. Interleukin-2 is a natural product that the body itself makes and is very important in maintaining what we call the homeostasis or the ability of the immune system to function properly. We call it a cytokine, because it evolves from a cell, in this case a T cell.

It can expand or amplify certain cells of the immune system. There's a study going on at the NIH that was originated at the intramural program at the NIH but is now being done in other centers throughout the country, where in a very specific way, the compound is administered intermittently to people who are HIV infected, and is actually expanding their level of immune competent cells that they find to be decreased as the disease goes on.

And the results have really been very encouraging. It's a classic example of why the clinical center at NIH in Bethesda is so important. Because it was the commitment to that very basic approach that worked its way into a clinical trial. This could not really have been initiated under any other circumstances. Now that the concept has been proven that can go out to the other medical centers. But I think if you want to pick out a real good example of why the clinical center is important, this would be one.

AIDS RESEARCH

Mr. MILLER. One more question, Mr. Chairman, and you may have covered this already. Having just talked to Dr. Paul, the whole issue of the AIDS research and what's done in your Institute and how it's all divided up in everybody's institute budget. What's your opinion of that, the consolidated budget? I think that's what

Dr. Paul favors, but what was proposed out of this committee was different. Do you want to comment?

Dr. FAUCI. Yes. The Office of AIDS Research as a coordinating entity has worked very well. I believe we've had a very good year. Dr. Varmus himself, actually, asked for the review of the Levine Committee, which has made some, I think, good suggestions about how we can even do better than we're doing. That implementation will occur in a coordinated way.

So I think things have worked quite well, very well, actually.

Mr. MILLER. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Miller.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

AIDS DEMOGRAPHICS

Dr. Fauci, it's always a pleasure to have a chance to have you appear before our subcommittee. I want to pose some questions to you relative to your particular part of the budget.

As you know, over a number of years, we've seen the faces of AIDS change. By that, I mean we've seen a shifting from gay males to a disease now which disproportionately affects women and minorities. This obviously has necessitated some changes, I would think, in the approach of your Institute relative to this disease. Can you tell us how this change, has been reflected from a research, research training and outreach standpoint?

Dr. FAUCI. Well, that's an excellent question, Mr. Stokes. You and I had conversations about this over the past few years, when we predicted that there would be this change in demography of the epidemic. And what we have done, from getting minority institutions involved in our AIDS clinical trial group to the development of a community program that has a very high accrual, relatively speaking, of women and minorities, and making an important part of the criteria of the judging of our clinical trial program the ability to access minorities into the program.

So that's something that isn't just wished for, that's an important requirement of what these units need to do. Remember the numbers years ago that we discussed. You were not happy with them because the relative proportion of people in our clinical trials were not even close to what the proportion of HIV infected African-Americans or Hispanics were.

The numbers now have reached and exceeded the relative proportion. As you know, of the 12.5 or 12.3 percent African-Americans in this country, that 32.5 percent of the AIDS cases are among African-Americans. We now have 34 or 35 percent of the accrual in our clinical trial processes African-Americans. So we've reached it and even gone beyond it. And the same thing holds true for women and Hispanics. And that took a lot of effort. We'd like to keep it that way and do even more on that. And there are a variety of other things.

But that's just an example of how we've modified our approach to be able to look square in the eye the changing of the demography of the epidemic.

AIDS IN CHILDREN

Mr. STOKES. You mentioned minorities and women. What about children? What's the situation now as it relates to children and the AIDS epidemic?

Dr. FAUCI. What's happened with children, is an interesting couple of curves that have superimposed upon each other. We now have approximately 7,000 total cases of HIV in children. The increase that we saw, the spurt, was a reflection of the heterosexual transmissibility that has gone from 1.9 percent per year in 1983 or 1984 to now over 13 percent of the new cases in 1994 and 1995 have been among heterosexual transmissibility. This naturally will give you more children who are infected.

So we clearly have a strong effort in pediatric HIV, as well as a considerable amount of effort in trying to understand and interrupt the transmission of HIV from an infected mother. I told you last year about the striking results with AZT which brought the infection transmissibility from 25.5 percent to 8.3 percent in HIV infected mothers.

As I mentioned a little while ago, with the newer drugs, the protease inhibitors alone or in combination, I fully expect that we may bring down that number to a very few percent, potentially to zero. Obviously we've got to get the health care delivery system to be able to have access to those people. But if we had good access to HIV infected mothers, we'd be able to literally have this disease disappear from the standpoint of transmissibility from mother to child. And that's something that we're looking upon with great optimism that we'll be able to do.

CLINICAL TRIALS

Mr. STOKES. Is your budget for fiscal year 1997 reflective of what you need to do in terms of clinical trials?

Dr. FAUCI. Obviously, we have a constrained budget, in that there are many things that we need to do. In the recommendations of the committee, the Levine Committee, as well as in our negotiations with the OAR, the emphasis is being torqued slightly, but I think it will be significant and appropriately so, towards basic research and investigator initiated awards.

When you have that occur out of necessity you're going to have a flattening and even somewhat of a decrease in the clinical trial process. And that is being reflected in both the adult and in the pediatric clinical trial process, where the amount of money that is put into, for example, the AIDS clinical trial group, is less than it was in the previous competition, because of this shifting of emphasis.

MINORITY HEALTH

Mr. STOKES. Now, Dr. Fauci, for a number of years, this particular subcommittee has been very much concerned about the gap between minority health and majority health in our country. And, it was to this particular subcommittee that, a number of years ago, the Secretary of Health and Human Services, which at that time was Health, Education and Welfare, presented the results of the

original year-long study that revealed about 85,000 excess deaths in the minority community.

In response, over a number of years, this subcommittee has done a great deal in terms of investing in programs to try and narrow that gap in minority health. Each year, I ask each of the institute heads, Dr. Varmus and others, about what gains are we making, or whether the gap is actually widening, as opposed to narrowing.

In terms of your Institute, can you tell us if we are making any gains in terms of narrowing this gap between minority and majority health?

Dr. FAUCI. I can give you one cogent example of that, that has a long history. And I won't give you a long story. I'll just summarize it as something that you've been very interested in, and that is, the inner city asthma program. This is essentially directed at African-Americans and Hispanics in the inner city area, where we had a couple of phases to it where we tried to identify those factors that were leading to an increase in hospitalizations and an increase in deaths, particularly among minorities in the inner city areas.

And with a combination of identifying factors, some of the fundamental science, but even more important, some of the outreach programs that have evolved from this program, this year, I'm happy to report, has led to a 30 percent decrease in hospitalizations from asthma in the individuals who fell into that program. I think that's a very important advance, and we need to do even better than that. Because it's still unacceptably high, and that's the reason why we have such a commitment to that. So that's, I think, a good practical example.

COLLABORATIVE EFFORTS

Mr. STOKES. Doctor, can you tell us what collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are you doing anything specifically with them?

Dr. FAUCI. Yes. We in fact are doing a number of things related both to our AIDS program, our program in the topical microbicides, and even most recently, we have an initiative in malaria research that they are coming in as full partners with us. We are very interested in pursuing the approach of cloning the genes of the malaria parasite to be able to better understand that pathophysiology of the microorganism, including drug resistance. And we've had a very good partnership that we've just recently established with the help of the facilitation by Dr. Varmus of being able to get us involved with them in that.

Mr. STOKES. Are any of these projects being co-funded by the Institute?

Dr. FAUCI. Yes, oh, definitely. That's how we're doing it. We're doing it in a co-funded way.

Mr. STOKES. Can you put into the record for us a list of of these projects?

Dr. FAUCI. Sure, I'd be happy to do that.

[The information follows:]

In FY 1995 the National Institute of Allergy and Infectious Diseases collaborated with the Office of Research on Women's Health and the Office of Research on Minority Health on the following programs:

Research, Training and Recruitment Initiatives Designed to Improve Minority Health.

Summit of HIV Research Agenda for African Americans.

Re-entry into Biomedical Research Career Program.

Mucosal Immunization Against Genital Transmission of HIV.

Perceived risk for Sexually Transmitted Diseases.

Mechanisms of Embryonic/Fetal Tolerance.

Biological Effects of Silicone.

Program Projects in Autoimmunity.

Immune Responses to Thyroid Peroxidase and Human TCR V Beta Gene Locus in Autoimmune Disease.

Acquisition of Immunity of Malaria in Cameroon.

Workshop on the development of Outcome Measures for Therapeutic Trails of Chronic Fatigue Syndrome.

Chronic Fatigue Syndrome Publication.

Sarcoidosis Study.

Mr. PORTER. Mr. Stokes, your time is up, but we're going to do a second round that will be about three minutes each, because we started late. And we'll get back to you.

Mr. STOKES. Thank you, Mr. Chairman.

Mr. PORTER. All right?

Mr. STOKES. Sure.

NIAID BUILDING FACILITIES

Mr. PORTER. Dr. Fauci, we understand that NIAID is going to move. And that you are moving prior to the expiration of the lease on the space you now occupy. Can you tell us what that's all about?

Dr. FAUCI. The Institute—you just gave me a premature ventricular tachycardia. [Laughter.]

Mr. PORTER. This is one of your buildings.

Dr. FAUCI. Yes, the Solar Building, that we have on Executive Boulevard, in Bethesda, has a lease that expires soon. And we are looking for a better arrangement right now. Mike, do you know where we are with that?

Mr. GOLDRICH. Actually, we have to work with the General Services Administration. We're right now in the stage of developing our requirements. For those who aren't aware of it, when we first moved into the Solar Building, many years ago, it was a state of the art facility.

But what's happened over the years is that we've had problems with some of the climate control and with some of the environmental issues. And actually, we're looking at a number of different locations where other NIH institutes are located now on Executive Boulevard and the surrounding area.

Mr. PORTER. But we understand this move is prior to the expiration of the lease, is that correct?

Mr. GOLDRICH. No, it's not correct.

Mr. PORTER. You're going to go after the expiration of the lease?

Mr. GOLDRICH. Well, it will coincide with the expiration of the lease. What's happening is, and sometimes people will get nervous because they will hear about negotiations, that GSA, almost 18 months in advance of the lease expiring, has asked us for our space requirements. That is the stage we are in right now.

Mr. PORTER. I see. We may have some other questions for the record on that one.

LEVINE PANEL

Mr. PORTER. Finally, Dr. Fauci, we talked about the Levine Panel evaluating your research efforts on AIDS and others. Do you feel that any of the recommendations would be inadvisable for your Institute to adopt?

Dr. FAUCI. Actually, the way we're looking at it and the way Dr. Varmus and I and the other institute directors and Dr. Paul are approaching it is that we're going to take it recommendation by recommendation, analyze it and determine if we can get to the bottom line of what they're trying to accomplish. Now, that may mean that certain specifics of certain recommendations might not be appropriate to implement to the letter for a variety of reasons. I'm sure that that's going to happen in some of those recommendations.

But I think the spirit of wanting to, for example, enhance a vaccine effort or put a great emphasis on investigator initiated research, I think in general we agree with the spirit. And what we need to do is find out if in fact we can best implement that, either precisely the way they're recommending, or if there's something that we can work out in an agreement with Dr. Varmus and the institute directors and Dr. Paul about how to get there.

So I don't think I can appropriately say, well, this is a bad one and this is a good one. I think they need to be discussed in the general context of how it impacts the program. And that will be an ongoing process that I'm sure you'll hear about.

Mr. PORTER. Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman.

STRAINS OF HIV

Dr. Fauci, I want to follow up on a line of questioning by my colleague, Mr. Stokes. Could you discuss the different strains of HIV and their implications for public health, for example the E strain and the implication for women?

Dr. FAUCI. Okay. Well, first of all, clearly, in any strain of HIV, it is much easier to transmit from a man to a woman than from a woman to a man. In fact, there was a study a few years ago that showed there was about an 18 to 19 times greater probability of in any given sexual encounter of a man who is infected giving it to a woman rather than a woman who is infected giving it to a man. There are a variety of physiological and anatomical reasons for that.

But there's also something that relates to the virus that is under intense scrutiny right now. The predominant, in fact overwhelmingly dominant strain in the United States is what we call a CLAD B or a B subtype. It's seen in the United States, it's seen in South America, although South America has a few other types. It's seen in Western Europe. In Africa, it's A, C and D, and in Thailand, it's predominantly E. It started off as D and a little E, and now E is taking over to be about 85 percent.

What that means is that there's enough differences in the virus to not make it a different HIV, but a different subtype. There was a recent study that asked the question of whether the predominance of heterosexual transmissibility in Thailand could be explained by a property of the virus.

So a study that was conducted in collaboration with the Thais by Max Essex and his group in Boston was to look at the capability of the virus to infect a particular type of cell that resides beneath the mucosa, of any mucosa, the vaginal mucosa, the oral mucosa, or what have you, called a Langerhans cell. And this group E, this CLAD E—

Ms. PELOSI. Langerhans?

Dr. FAUCI. Langerhans, yes.

Ms. PELOSI. As in the pancreas?

Dr. FAUCI. Yes. Same guy, he did a lot of work. [Laughter.]

What he showed was that the CLAD E was able to more readily infect Langerhans cells than a CLAD B. Now, the leap that was made, and I have to say leap, I don't mean that in a derogatory way, but the assumption was then perhaps if it can infect submucosal cells more easily that that's the reason why heterosexual transmissibility is so predominant in Thailand. I think we have a long way to go before we can even begin to say that's the case. Because there are several observations that essentially destroy that paradigm. One of them is in Haiti and in South America, which is also predominantly B, where heterosexual transmissibility is the major modality of transmissibility. Also, the demographics and the dynamics of the epidemic and how it's spread in Thailand is much different than the United States. So I do not reject at all as a scientist the possibility that this might contribute.

But we have to make sure that we emphasize to people that whether it is or is not transmitted better with one CLAD versus another, you still should be practicing safe sex. I mean, it would be foolish to say, well, there's a CLAD B in society and CLAD E is more easily transmitted, so I don't have to worry about heterosexual transmissibility. That's one of the things that I'm afraid of as a public health person, that people will assume that there's a greater or lesser danger, and either slacken or what have you, their precautions about sexual contact.

Ms. PELOSI. I appreciate that, and of course it's an issue since heterosexual transmission is a major issue in the minority community. I'm following this issue.

I have a question about something you said earlier about the combination therapy, and I want to make sure I understood it correctly, that it was so effective that it, the impact that it had on the blood was that it, you couldn't detect—

Dr. FAUCI. The virus in the blood, yes.

Ms. PELOSI [continuing]. The virus in the blood. Does this pose a challenge to us in terms of testing?

Dr. FAUCI. No, absolutely not. Because—

Ms. PELOSI. We have people who already have—

Dr. FAUCI. Well, you see, again, that's the distinction between detecting the virus and detecting an antibody to the virus. If a person's HIV positive and they have a million copies of the virus in their blood, they will be HIV positive. If you bring the virus down to a very low level, they still will be HIV positive. The only way they may, after years and years, revert to negative, is if you completely eliminate the virus from the body, and after a long period of time, your antibody level will go very low.

But even that is very unlikely. Because we have antibodies in our system to polio, to tetanus, things that we just don't have in our system. And yet, you maintain immunological memory. So I don't think that we need to worry that if you eliminate the virus or bring it down to a low level that that's going to have any impact on the diagnostic test for antibody of HIV.

LEGIONNAIRE'S DISEASE

Ms. PELOSI. Recently, we had a scare in—this is another subject—we had a scare in San Francisco with a possible outbreak of Legionnaire's disease in the Federal Building. Thankfully, Occupational Safety and Health Administration acted quickly to identify the organism, isolate the problem and by raising the temperature of the water, eliminating the risk. I know I don't have much time, but could you briefly explain, I know you addressed Legionnaire's disease in your full report, how it works and how it can be prevented. It was really a scare.

Dr. FAUCI. It certainly is. In fact, as was the original Philadelphia episode, where we became aware of Legionnaire's disease. This is a microbe, a bacteria, that can spread through the air. When it gets into a system where you have multiplication of it in a particular site, like in a heating system or in a water system or what have you, and you have poor public health measures, either in air purification or what have you, or if you have a broken down air flow system, you can have spread of this microbe to a number of people.

Fortunately, we now in 1996 can easily diagnose it, and it's an eminently treatable bacteria. It's quite curable with antibiotics. The difficulty is that some form of Legionnaire's disease can give you a fulminant pneumonia. And if a physician is not thinking about it and someone comes in, they may not treat them with the right antibiotic. That's the problem.

Ms. PELOSI. I don't know if we'll have another round, so I did want to take this opportunity to thank you for your testimony and for your good work. I'm very excited in what I consider to be a breakthrough. [Laughter.]

I can say that, you cannot, on your good work this year, and, on the years leading up to what you were able to announce this year. You're still more than ever living up to President Bush's characterization of you as a hero. Thank you, Dr. Fauci.

Dr. FAUCI. Thank you.

Ms. PELOSI. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Miller.

PROTEASE

Mr. MILLER. To follow up on this question of breakthrough versus advance, or what you call a big advance. Will protease ever lead to a breakthrough? Or where would the breakthrough come from? I mean, where are you advancing?

Dr. FAUCI. I think it's a matter of semantics, Mr. Miller. But I would comfortably be able to come here in front of this committee and say, this is a breakthrough, when the clinical trials show that you actually have an important impact on the longevity of a person

and on the quality of life over a period of years, where I can say, I have a patient of mine who comes in relatively early in the course of disease, I treat them with combination therapy and ten years later, five years later, their CD4 count is normal, you can't detect the virus, that's a breakthrough.

Mr. MILLER. So it's possible, for example, with protease, that with more time——

Dr. FAUCI. It is conceivable——

Mr. MILLER [continuing]. The results will be able to confirm what?

Dr. FAUCI. We may have a breakthrough on our hands that we haven't proven is a breakthrough yet, but which will ultimately turn out to be one.

LEVINE REPORT

Mr. MILLER. Okay, thank you.

Let me ask you a question about the Levine report. Dr. Paul gave me a copy of it, and I haven't looked at it. But would you briefly, I don't know how much time we have, explain to me a little bit more about the creation of it, or maybe Dr. Varmus would, why it was created and what were the purposes or goals and the results, very briefly, of what it came out with?

Dr. FAUCI. Yes. In fact, I could have Dr. Varmus, who essentially was very much involved in taking, which people have characterized, and I think appropriately so, as a courageous step towards opening up and saying, we've been doing a lot of work, we believe we've been doing a good job, a very good job, but let's take a look at how we can do better. And that was what we have, a spirit at the NIH, not only in AIDS research, of being able to have outside reviewers scrutinize what we do. I think we do an excellent job.

But I think we can always do better. And that's how you strive for excellence, is by opening yourself up to do better. And that really is the fundamental spirit of the review. Have someone who is not an involved party come in, get the best people you possibly can, get a lot of them, and say, here, take a look at what we're doing and make some recommendations. And that's exactly what they did. And now we're in the process of examining those recommendations and seeing if we can in fact make things better based on them.

Dr. VARMUS. Shortly after Dr. Paul assumed the position as Director of OAR, we had a series of what we called "kitchen cabinet" meetings with a number of leading investigators in the AIDS community. It was recognized that new authorities had been given to the OAR through the Reauthorization Act of 1993 and that the entire AIDS program had never been reviewed in a global sense, looking at all the activities of all the institutes and all the disciplines that affect our studies of HIV and AIDS. It was therefore recommended that Dr. Paul and I commission a very large review of the entire program, so that as we go forward under these new authorities, we have a reasonable assessment of what's happened in the last 10 years.

It was a very fortuitous time to do that, because as you've been hearing, major advances have occurred in the last year. This is a time to reevaluate where we are and to think about new directions.

Mr. MILLER. You call it a major advance, he called it a big advance, but neither of you has a breakthrough.

Dr. VARMUS. Advances. [Laughter.]

Mr. MILLER. Okay, great.

Mr. PORTER. Thank you, Mr. Miller.

Mr. Stokes.

CHILDREN AND COMBINATION THERAPY

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Fauci, how do children fit into this combination therapy equation? Or do they?

Dr. FAUCI. Well, they certainly do. The initial trials have not been done on children. But as you know, years ago it became very, very clear that in AIDS we would not have that traditional dichotomy between AIDS and children. And right now, we're going to be seeing trials that are going to be demonstrating, I'm sure, effectiveness in children.

The real question with the child is not necessarily is it going to be as effective, but in fact, is it going to be safe in the child. But that's something that is very actively being pursued right now.

PEPTIC ULCER DISEASE AND GASTRIC CANCER

Mr. STOKES. Now, am I correct that your Institute is doing some work on peptic ulcer disease and gastric cancer?

Dr. FAUCI. Right.

GASTRIC CANCER IN MINORITIES

Mr. STOKES. What are you doing particularly as it relates to a higher incidence of gastric cancer in minorities?

Dr. FAUCI. Indeed. We have a collaborative arrangement with NIDDK, which you'll hear from in a short while, in which we are jointly sponsoring a Request for Applications to look specifically at the question that you alluded to, Mr. Stokes, is there greater incidence of gastric ulcer and gastric cancer related to H pylori in minority individuals. So we have a study that we are going to be doing in a collaborative way with NIDDK.

OUTREACH AND PUBLIC EDUCATION

Mr. STOKES. Okay. With respect to outreach and public education, how much are you doing in your Institute?

Dr. FAUCI. Well, actually, I think we're doing a fair amount. I'm proud of what we're doing. We have a number of outreach programs to minority institutions. We have our introduction to biomedical research from our Institute that has been very successful that we've done now for a number of years, and it continues to be very successful and very popular among minority students.

We have a bridging the gap program, which we bring in individuals who we are trying to steer towards getting involved in the mainstream of biomedical research. We have our outreach in our clinical trial process that I alluded to just a few minutes ago. In fact, we have a fedex molis computerized internet type of approach of accessibility of all job offers or job availabilities in academia, in NIH, that is specifically directed towards minorities in order to

make them aware of these job offers as they come up. I think we're doing everything from actual health related issues to recruiting of people into the mainstream.

Mr. STOKES. Thank you, Dr. Fauci.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

We have additional questions for the record, Dr. Fauci.

We want to thank you for your testimony this morning. You're doing an excellent job, both the science and the management, and we very much appreciate the wonderful work that you do there.

Thank you for appearing.

Dr. FAUCI. Thank you very much.

[The following questions were submitted to be answered for the record:]

LEVINE PANEL

Mr. Porter: The Levine panel recommended the creation of a separate vaccine development division within your Institute headed by a non-government scientist. Do you expect to establish such a division, and is it consistent with the plan you recently developed for vaccine development with industry?

Dr. Fauci: We are pleased with the recommendations relating to increased focus and effort in HIV/AIDS vaccine research. We believe that the panel's recommendations are compatible with our strategy of private-public sector collaboration. Currently, we are carefully reviewing each specific recommendation from the Levine panel with the NIH Office of AIDS Research and we are formulating implementation plans.

AIDS CLINICAL TRIALS

Mr. Porter: Last September, Science magazine carried an article regarding the difficulty of conducting AIDS clinical trials due to patient dropout, the difficulty of isolating the impact of a single drug when patients may be self administering others, etc. Have these problems compromised the reliability of the AIDS clinical trials you conduct?

Dr. Fauci: We have every confidence in the reliability of the clinical trials conducted so far. Through our use of advanced statistical methodologies, we can minimize the impact of participant dropout by establishing a target recruitment goal that takes into account an estimated rate of dropout. This built-in safeguard allows for a certain amount of dropout without jeopardizing our ability to answer the trial's primary question. In general, if the number of participants in any one clinical trial falls below the calculated amount necessary to answer the primary question with enough power to detect statistical differences, then we carry out appropriate interventions. These may include stopping the trial, extending recruitment beyond the original period, redesigning the protocol, answering only those primary or secondary questions we can answer with the data given, developing strategies to increase patient participation, and opening the clinical trial up to other research mechanisms that may help in enrollment.

The issue of self-administration of interventions and the impact on clinical trials results is an important one. However, this is not a new issue in clinical trials. Concomitant uses of alternative, complementary, approved, or unapproved therapies have been an issue in clinical trials since there have been clinical trials. Our goal is to minimize the impact, or interference in the ability to answer the primary question(s) of the main clinical trial. We use several methods to minimize this impact. One basic assumption is that through randomization, use of non-study interventions will be equal across all study arms, thereby decreasing the effect when assessing the study agent. Strong participant-study personnel relationships will increase the chance of more thorough disclosure of non-study intervention usage. Designing individual clinical trials to allow co-enrollment in other trials has been effective, as has been developing newer methods of assessing sequential therapies over time that more closely mimic interventions seen in the primary care setting.

One of the most important aspects of dealing with the issues discussed is the involvement of community representation in the design and conduct of clinical trials sponsored by the NIAID. Input by affected communities and persons with HIV disease in this process has allowed for the design and conduct of trials that are more likely to be completed with lesser effects of the above described issues. Designing clinical trials in the rapidly changing setting of HIV disease presents many challenges. However, the purpose of clinical trial research is not solely the carrying out of a clinical trial, but also continued research in clinical trial methodology, to which we are also committed.

PRIMARY IMMUNE DEFICIENCY RESEARCH

Mr. Porter: Earlier this year, the subcommittee heard testimony from representatives of the Jeffrey Modell Foundation which funds primary immune deficiency research. I understand that NIAID has entered into a collaborative effort with the Foundation to fund research into this disease at a level of \$500,000 per year for five years. How is this collaboration working so far? Have you begun to receive proposals from researchers?

Dr. Fauci: Our collaborations with the private sector are working very well. In March 1995, we published a joint program announcement with the Jeffrey Modell Foundation on gene therapy for primary immune deficiency diseases. We have been receiving applications in response to this announcement and we funded the first grant in March 1996. We anticipate funding a second grant later in FY 1996.

JOINT COLLABORATIONS

Mr. Porter: Do you see this approach as a means of stretching Federal research dollars that might be replicated by other foundations and associations?

Dr. Fauci: We believe that our joint collaborative approach will result in several important outcomes. Specifically this approach will enable the NIAID to fund more research grants in this area than would otherwise be possible, thus stretching Federal research dollars; reduce duplication in research efforts between the public and private sector both as to specific areas of research and in administrative costs; and encourage a more cohesive research agenda. We are also working with other organizations such as the Juvenile Diabetes Foundation International to accomplish similar goals.

H. PYLORI INFECTION

Mr. Porter: In 1994, the NIH consensus development conference endorsed the findings that H. Pylori is strongly associated with peptic ulcers. Was your institute involved in the research that led to this finding? Are you involved in any public education efforts in this regard?

Dr. Fauci: The NIAID was involved in studies on the basic pathogenesis and immune response to H. Pylori infection, the development of animal models of disease,

and the development of a rapid serology test capable of detecting infected individuals. NIAID-funded individuals continue to be major contributors to our knowledge of this organism.

The NIAID continues to emphasize the importance of *H. pylori* research. We have published two Program Announcements, one in 1993 and one in 1995, calling for applications in this area. These program announcements have contributed to our identifying and funding of new investigators in this field, thereby strengthening the research infrastructure and base of information that will reap payoffs for years to come. In FY 1997 we plan to cosponsor an initiative on *H. Pylori* in minority individuals with other NIH institutes.

The NIAID has been actively involved in educational activities related to *H. Pylori*. We co-sponsored the important Consensus Development Conference with NIDDK in 1994 that recommended that physicians use antibiotic treatment to treat and cure ulcer disease. We have actively distributed this document and speak about its conclusions at every public opportunity.

CHRONIC FATIGUE SYNDROME

Mr. Porter: Please provide a complete list of intramural CFIDS (CFS) research projects currently funded by NIH and funding totals for each project. Where appropriate, please provide a report on any promising results identified by each research project.

Dr. Fauci: We have provided the requested list of NIH funded intramural CFS projects below.

National Institute of Allergy and Infectious Diseases

INTRAMURAL PROJECTS RELATED TO CHRONIC FATIGUE SYNDROME

<u>Project Title</u>	<u>Amount</u>
Chronic EBV Infection & Chronic Fatigue Syndrome	\$658,000
Total NIAID Intramural Chronic Fatigue Syndrome	\$658,000

National Cancer Institute

INTRAMURAL PROJECTS RELATED TO CHRONIC FATIGUE SYNDROME

<u>Project Title</u>	<u>Related Amount</u>
Identif. of Hum. Genetic Loci Which Influence Susceptibility to HIV	\$15,000
Regulation of Vial and Cellular Gene Expression	\$30,000
Identif. of Hum. Genetic Loci Which Influence Susceptibility to HIV	\$100,000
Genetic Variation in Infected Hemophiliacs Over Time	\$30,000
Total NCI Intramural Chronic Fatigue Syndrome	\$175,000

National Institute of Mental Health

INTRAMURAL PROJECTS RELATED TO CHRONIC FATIGUE SYNDROME

<u>Project Title</u>	<u>Amount</u>
Role of the CNS in the Susceptibility to Inflammatory Illness	\$456,000
Stress-responsive neurohormone in the pathophysiology and Pathogenesis of Depression	\$380,000
Clinical Aspects of Winter Seasonal Affective Disorder (SAD)	\$152,000
Total NIMH Intramural Chronic Fatigue Syndrome	\$988,000

Research Results From NIH Funded Intramural CFS Projects:

NIAID

Dr. Fauci: NIAID Intramural scientists have been conducting a broad range of studies of CFS since 1979. These studies have covered multiple investigations for potential viral causes and cofactors in the syndrome. We have also conducted neurologic studies of brain function, neuropsychologic studies of mood and memory, studies of allergies in CFS, neuroendocrine studies, and therapeutic trials.

Within the past year, NIAID intramural CFS investigators have accomplished the following:

We completed a three year placebo-controlled trial of hydrocortisone therapy for CFS. We are now analyzing the data and we will report our findings in the Fall of 1996.

We completed a four year longitudinal study of lymphocyte phenotype and function in CFS.

We initiated a collaborative, two center, placebo-controlled, trial of fludricortisone in CFS, with Johns Hopkins University.

We have also completed several collaborative studies with other Institutes of the National Institutes of Health.

These include:

We completed a controlled study of arginine-vasopressin infusions with the National Institute of Mental Health. This chemical stimulates the pituitary-adrenal axis and is helpful in delineating abnormalities in these hormonal pathways.

We have completed and published focussed studies of memory with the National Institute of Neurological Disorders and Stroke.

We completed and have submitted for publication a study of signal processing and muscle responses with the National Institute of Neurological Disorders and Stroke.

NIMH

Dr. Hymen: The Clinical Neuroendocrinology Branch studies mechanisms of physical and emotional stress and their relevance to health and disease. Their data has previously suggested that patients with chronic fatigue syndrome show a deficiency of the stress hormone cortisol that in other contexts has been shown to be associated with states of lethargy and fatigue. To explore the mechanism of this decrease in cortisol, they developed a clinical research paradigm (graded treadmill exercise) whose application produces a dose dependent activation of stress hormones that is independent of the subject's prior exposure to the stressor (i.e., physical conditioning). This paradigm allows us to investigate the functional integrity of brain stress systems, especially of the arousal producing neurohormone CRH, which is also responsible for regulating cortisol secretion. Our studies demonstrate that in addition to a cortisol deficiency, patients with chronic fatigue syndrome also show a CRH deficiency. This deficiency of an arousal producing hormone could also contribute to lethargy and fatigue in patients with chronic fatigue syndrome and provide a central nervous system target for novel pharmacologic interventions for this disorder. Dr. Philip Gold, the principal investigator of this work, was recently invited to present his work on fatigue states to a Beth Israel Hospital Seminar in Medicine at the Harvard Medical School which will appear in the New England Journal of Medicine as "The Neurobiology of Fatigue."

The clinical profile of seasonal affective disorder (SAD), a recurring condition of winter depressions and summer remissions, and light therapy, which the NIMH first found to be an effective treatment for SAD, has become a mainstream psychiatric treatment. The NIMH continues to explore aspects of the clinical profile of Seasonal Affective Disorder or SAD patients. One study evaluated sensitivity to environmental chemicals and compared responses to other patient groups and controls. A standardized self-administered questionnaire was administered to patients with chronic fatigue

syndrome (CFS), obsessive compulsive disorder, Addison's Disease, Cushing's Syndrome, and controls. Patients with SAD, Addison's Disease, and CFS reported highest sensitivities to exposure to various environmental chemicals and to a significantly greater degree than those in the other groups. In general, women reported greater chemical sensitivity than did men.

Mr. Porter: Please provide a complete list of extramural CFIDS (CFS) research projects currently funded by NIH. Please indicate which projects seek to identify the etiological agents and markers for and the pathophysiology of CFIDS (CFS)?

Dr. Fauci: We have provided a list of Extramural CFS projects funded by NIH below.

National Institute of Allergy and Infectious Diseases
EXTRAMURAL PROJECTS RELATED TO CHRONIC FATIGUE SYNDROME

<u>Project Title</u>	<u>Amount</u>
<u>CFS Cooperative Research Centers</u>	
Chronic Fatigue Syndrome Cooperative Research Center	\$563,000
Comparative Study of Pathophysiologic Descriptors of CFS	\$586,000
Chronic Fatigue Syndrome Cooperative Research Center	\$100,000
Syndromic Approach to the Chronic Fatigue Syndrome	\$970,000

All of the projects listed in the subheading above are related to the etiological agents and markers for the pathophysiology of CFS.

Exercise/Cytokine Grants

Exertion-induced Cytokines in CFS	\$175,000
Mechanisms of Immunologically Mediated Fatigue	\$223,000
Exercise Intolerance in CFS	\$159,000
Motor Control and Cytokines in CFS	\$150,000

All of the projects listed in the subheading above are related to markers for the pathophysiology of CFS.

Viruses

Antigens of Human Herpesvirus-6	\$142,000
JHK Virus	\$269,000
Virology and Immunology of CFS	\$166,000
Pathogenesis of Epstein-Barr Virus Infections	\$359,000

All of the projects listed in the subheading above are related to the etiological agents and/or markers for the pathophysiology of CFS.

Epidemiology/Medicine/Sociology

Estimating Rates of CFS in a Community Sample	\$591,000
Social Processes and Somatization--The Course of CFS	\$141,000
Total NIAID Extramural Chronic Fatigue Syndrome	\$4,594,000

National Cancer Institute**EXTRAMURAL PROJECTS RELATED TO CHRONIC FATIGUE SYNDROME**

<u>Project Title</u>	<u>Related Amount</u>
Transforming Domain of HHV 6 that Transactivates HIV 1	\$207,000
Viruses and Oncogenes in Hematopoietic Malignancies	\$102,000
Epidemiologic Study of Pediatric HIV related Lymphomas	\$55,000
Molecular Studies on BIV and BHV Interactions	\$21,000
Total NCI Extramural Chronic Fatigue Syndrome	\$385,000

All of the above extramural projects are related to the etiological agents and markers for the pathophysiology of CFS.

National Institute of Arthritis and Musculoskeletal and Skin Diseases
EXTRAMURAL PROJECTS RELATED TO CHRONIC FATIGUE SYNDROME

<u>Project Title</u>	<u>Related Amount</u>
Function(s) of Simple Epithelium Keratins	\$24,000
CTL Mediated Cutaneous Immunity to Melanoma	\$92,000
Molecular Determinants of Epstein Barr Virus Tropism	\$92,000
Molecular Basis of T-cell Helper Function	\$47,000
Total NIAMS Extramural Chronic Fatigue Syndrome	\$255,000

All of the above extramural projects are related to the etiological agents and markers for the pathophysiology of CFS.

National Institute of Mental Health
EXTRAMURAL PROJECTS RELATED TO CHRONIC FATIGUE SYNDROME

<u>Project Title</u>	<u>Amount</u>
Research Center on the Psychobiology of Ethnicity	\$965,000
Total NIMH Extramural Chronic Fatigue Syndrome	\$965,000

The above extramural project is related to the markers for the pathophysiology of CFS.

Mr. Porter: In the recompetition of the CFIDS (CFS) Cooperative Research Centers, two center grants were funded, compared with three center grants in the previous grant period. Will the total level of funding increase, decrease or remain the same? Has any consideration been given to expanding this program before the next recompetition?

Dr. Fauci: In FY 1995 the NIAID recompleted the Chronic Fatigue Syndrome Cooperative Research Centers. We funded two centers for \$1.4 million compared with three centers for \$1.8 million before the recompetition. We also made phase-out funds available to the Centers that did not compete successfully so that they could complete ongoing studies.

We do not anticipate that we will expand the CFS Centers program before the next recompetition. However, CFS Center Director's meetings include invitations to other CFS scientists whose research is related to the studies that we are undertaking at

the CFS Centers. Thus, multidisciplinary research on CFS takes place outside the CFS Cooperative Research Centers and we integrate this research when appropriate with the Centers program.

Mr. Porter: Does the NIH CFIDS (CFS) Coordinator, currently have institute-wide authority to coordinate budgetary issues and advisory council activities related to CFIDS (CFS)? If not, please provide a status report on efforts to address the suggestion made in last year's report that the coordinator be vested with Institute-wide authority?

Dr. Fauci: In FY 1991 appropriations report language, the Congress specified that NIH designate a CFS coordinator. In response, Dr. William Raub, Acting Director, NIH designated the Director, Division of Microbiology and Infectious Diseases (DMID), NIAID as the NIH CFS Coordinator and established the NIH CFS Coordinating Committee (NIH CFSCC). The NIH CFS coordinator chairs the NIH CFSCC and ensures that we exchange scientific information among staff from the relevant NIH Institutes.

The NIH Director is vested with institute-wide authority to coordinate budgetary issues and advisory council activities among and between the NIH Institutes. The NIH Director and the Institute Directors use multiple forums and methods to communicate and coordinate the setting of research and budget priorities.

Mr. Porter: What has been the outcome of efforts to involve institutes other than NIAID in CFIDS (CFS)-related research?

Dr. Fauci: Through the NIH CFSCC we have discussed the scientific opportunities for CFS research and have acted to organize workshops and issue program announcements to make investigators across multiple medical disciplines aware of the nature of CFS and of research opportunities that exist.

Among these activities has been the co-sponsorship of several CFS-related workshops including workshops on "Clinical Management" and "Development of Outcomes Measures for Therapeutic Trials." We have also co-sponsored two multi-Institute CFS Program Announcements. These include "New Insights in CFS" issued in August 1994 and "CFS Pathophysiology" planned for the Fall of 1996.

To involve representatives from other NIH Institutes and other government agencies in CFS activities fully, we invited members of the NIH CFSCC to attend the September 12, 1995 NIAID Council review of the CFS program.

Mr. Porter: Please provide a report on the NIAID Council's session dedicated to a review of CFIDS (CFS) research. What implications does this have for the future of CFIDS (CFS) research at NIH?

Dr. Fauci: We provided a copy of the CFS Research Program review in March 1996 to Representatives Porter, Obey and Miller and Senators Specter, Reid and Harkin.

We can summarize the comments of the Council Subcommittee as follows: The Subcommittee commended NIAID for its leadership in establishing a multidisciplinary approach to studying CFS. They noted that CFS research was still in its infancy and that we were developing and testing new hypotheses about etiology and pathophysiology. The Subcommittee recommended that until there is more definition of the fields of medicine most applicable to CFS research that NIAID retain overall NIH leadership and continue encouraging multidisciplinary research approaches.

The Subcommittee praised the Intramural program for the depth and extent of their research and for their involvement of other investigators both at other NIH Institutes and extramurally.

The Subcommittee recommended that we continue our extramural program's multidisciplinary approach and our interactions with other NIH Institutes and DHHS agencies when etiologies and hypotheses involving their mission and expertise come to the fore.

Finally, the Subcommittee recommended that NIH funding focus on hypothesis-driven, multidisciplinary research efforts. They suggested that we study the physiologic, endocrinologic and neurologic alterations in CFS and the immunologic manifestations of chronic illness.

DEPARTMENT OF DEFENSE AIDS RESEARCH

Mr. Porter: Tell us what type of AIDS research DOD is supporting and how it differs from the research your Institute is conducting. Does it make sense for them to be investing in this area as well as NIH?

Dr. Fauci: While we cannot speak to the specific content of DOD AIDS research, the DOD does conduct a broad range of AIDS research, as does the NIAID. This includes basic, therapeutic and vaccine research. A significant difference in the research that the DOD conducts is the population they serve. Through their clinical and vaccine trials network, the DOD has access to different populations than does the NIH, namely military personnel and their dependents. When working in collaboration the combined networks and other resources of the DOD and the NIH have greater potential for the rapid recruitment of participants into clinical trials and the expansion of important laboratory studies.

Mr. Porter: How do the DOD clinical trials relate to the network of trials you support?

Dr. Fauci: The clinical trials supported by the DOD are distinct from those trials supported by the NIH and NIAID, in particular. This is due to the separate and distinct funding and administrative structures of the two agencies. However, the NIAID and DOD have signed a Memorandum of Agreement to pursue several collaborative projects. Examples of these include:

A pilot study to evaluate the efficacy of ZDV in preventing CD4+ lymphocyte decline in patients with primary HIV infection.

A multi-center, open-label study of viral burden in peripheral blood vs. lymphoid tissue before and after antiretroviral therapy in HIV-infected individuals without AIDS

A prospective evaluation of the emergence of resistance to mono and combination nucleoside therapy in patients with less than or equal to three months of prior therapy.

A double-blind, randomized trial comparing ZDV, ZDV + ddI, and ZDV + ddI + NVP in asymptomatic patients on ZDV monotherapy who develop a mutation at codon 215 of HIV reverse transcriptase in plasma associated viral RNA.

Mr. Porter: What is the involvement of the Henry Jackson Foundation in conducting DOD AIDS Research?

Dr. Fauci: NIAID has had a Memorandum of agreement with the Henry Jackson Foundation to support the collaborative activities outlined above. Scientists from the foundation have contributed to the Institute's clinical trials programs, particularly, the AIDS Clinical Trials Group and the Terry Bein Community Programs for Clinical Research on AIDS by serving on scientific committees and as protocol chairs.

Mr. Porter: Did the Levine review panel make any recommendations about DOD AIDS Research?

Dr. Fauci: In the final draft of the "NIH AIDS Research Program Evaluation Working Group of the Office of AIDS Research Advisory Council" the Levine Panel did not make any specific recommendations about the DOD research efforts; their focus was primarily on NIH's institutes. Some of their recommendations, however, are directed at all government agencies, which would include the DOD. For example, the report calls for establishing a National AIDS Vaccine Task Force to coordinate all government-sponsored HIV vaccine programs. It is our sense that DOD would need to be included in any such task force given their efforts in HIV vaccine research.

PROJECTED SPENDING

Mr. Porter: Please identify FY 95-97 spending on the following: Lyme disease, chronic fatigue syndrome, vaccine development, tuberculosis, sexually transmitted diseases, asthma, topical microbicides, and AIDS clinical trials (with adult and pediatric shown separately).

Dr. Fauci: The following table displays the information, for NIAID, for the requested disease areas for FY 1995 through FY 1997.

	<u>FY 1995 Act.</u>	<u>FY 1996 Est.</u>	<u>FY 1997 Req.</u>
Lyme Disease	10,661,000	11,087,000	11,309,000
Chronic Fatigue Syndrome	5,252,000	4,810,000	4,906,000
Vaccine Development	183,808,000	196,971,000	206,975,000
Tuberculosis	34,252,000	35,252,000	35,959,000
Sexually Transmitted Diseases	66,972,000	69,651,000	71,044,000
Asthma	13,024,000	13,545,000	13,816,000
Topical Microbicides	11,731,000	12,200,000	12,444,000
	<u>FY 1995 Act.</u>	<u>FY 1996 Est.</u>	<u>FY 1997 Req.</u>
AIDS Clinical Trials			
Adult	157,701,000	161,918,000	161,826,000
Pediatric	<u>48,561,000</u>	<u>49,535,000</u>	<u>47,097,000</u>
	206,262,000	211,453,000	208,923,000

NIAID SPACE FACILITIES

Mr. Porter: When does the lease expire on your facility at 6003 Executive Boulevard in Rockville, MD?

Dr. Fauci: The lease on the facility at 6003 Executive Boulevard expires on January 31, 1998.

Mr. Porter: How long have you occupied that facility? How many institute, employees are located there?

Dr. Fauci: The NIAID has located staff in this facility since 1987 when we moved the AIDS Program to this location. Subsequently, we moved the remainder of the Institute's Extramural Divisions to this facility. Currently we have approximately 460 employees at this location.

Mr. Porter: What are your current lease costs? Do you incur any additional costs, such as utilities, etc.; related to the facility itself?

Dr. Fauci: The Division of Space and Facility Management (DSFM) pays our lease costs directly to the General Services Administration (GSA). The DSFM, in turn, charges the NIAID for the rent. Currently the DSFM pays the GSA \$2,374,556 per year for this facility. We also pay \$25,000 and \$225,000 per year for supplemental air conditioning and security services respectively.

Mr. Porter: Do you plan to extend the lease or recompet it?

Dr. Fauci: The GSA has informed us that extending the lease is not an option. The GSA will be recompeting the lease as a full and open procurement.

Mr. Porter: If you moved, would you leave prior to the end of the lease? Would you continue rent payments through the end of the lease in that event.

Dr. Fauci: The GSA is negotiating the new lease. They are attempting to accomplish this within a period that will allow us to move in October or November of 1997. The GSA has assured us that we will pay rent only for space we occupy. Since the GSA is the holder of the lease, they must negotiate directly with the landlord regarding payment for any unoccupied space after our departure should it occur before January 31, 1998.

Mr. Porter: Have you identified any problems with the current facility - Inadequate square footage, poor space configuration, ventilation, etc.?

Dr. Fauci: The existing facility has many major problems that jeopardize the health and safety of the staff at that location. The building does not meet recent building code requirements and does not meet Federal Safety and Security requirements.

For example:

- 1) The facility lacks a fire suppression system. Current code requires that all office buildings have a sprinkler system.
- 2) The U.S. Public Health Service has examined the adequacy of the Heating, Ventilation and Air Circulation System, and they have identified many deficiencies in the existing building systems.
- 3) The NIH Office of Research Services has surveyed the existing security systems and has judged them to be inadequate in meeting federally mandated security requirements.
- 4) Professional space planners have identified major inefficiencies in the configuration of the building's office space. We have looked into our options regarding space usage, and they have told us that we require major renovations to correct the problems.
- 5) As a whole, the facility does not meet the requirements of the Americans with Disabilities Act. The existing entry doors do not provide ease of access for persons with disabilities, and the restrooms do not meet Uniform Federal Accessibility Standards.

To meet the minimum requirements for federal occupancy, the building will require major renovations.

Mr. Porter: If you move out of the facility, what are the estimated moving costs? Do you incur those costs or does GSA?

Dr. Fauci: Because the expiration of an existing lease held by the GSA causes this move, they are responsible for paying all moving expenses. The exception to this is the cost of moving systems furniture and providing for telecommunications. We estimate that these costs will be approximately \$75,000 and \$736,000, respectively.

Mr. Porter: What is the GSA procedure for competing leased space?

Dr. Fauci: Acquisition regulations require "full and open competition" when acquiring leased space. Justification for lease negotiations on a non-competitive basis is extremely limited and cannot take place without first obtaining approval from senior officials.

Mr. Porter: Would the current landlord be eligible to compete?

Dr. Fauci: The current landlord is eligible to compete and his offer will be evaluated, along with all other offers having a reasonable chance of receiving the contract award, to determine which offer is in the best interest of the government.

Mr. Porter: Do you or does GSA make the decision on the winning bid?

Dr. Fauci: The GSA Contracting Officer will make the final decision on the selection of the winning offer.

Mr. Porter: Is there available GSA-owned space in the geographic area where you need to be located?

Dr. Fauci: According to the General Services Administration there is no federally owned space in the area of 6003 Executive Blvd. That would accommodate the space needs of the Institute.

Mr. Porter: How much usable square footage do you occupy in the current facility, and how much have you identified as your need for the next lease?

Dr. Fauci: We are occupying approximately 102,000 square feet in this facility. Working with GSA contractors, we have just completed a survey of our existing facility and have determined that, depending on the layout, we can best meet our needs with 100,000 to 106,000 square feet.

Mr. Porter: What are the square foot costs for other Institutes' leased space in the same area?

Dr. Fauci: The square foot costs for other Institutes' leased space in the same area are as follows:

<u>GSA Rent</u>		<u>Charges</u>
<u>Location</u>	<u>Rent w/Lessor</u>	<u>to NIH</u>
6000 Executive Blvd.	\$17.78	\$17.34psf
6006 Executive Blvd.	\$25.53	\$19.63psf
6006 Executive Blvd.	\$21.35	\$19.63psf
6011 Executive Blvd.	\$17.79	\$21.01psf
6100 Executive Blvd.	\$17.16	\$31.26psf
6120 Executive Blvd.	\$25.71	\$31.88psf
6130 Executive Blvd.	\$27.02	\$31.88psf

Mr. Porter: Do you have a specific facility or location in mind for your next lease?

Dr. Fauci: We do not have any specific facility in mind. The GSA has been clear that the lease competition must be a full and open procurement.

Mr. Porter: Compare the projected annual cost of your next lease if you move to another facility versus staying where you are versus your current lease.

Dr. Fauci: We are anticipating no change in annual cost. The GSA has said that we should plan to pay the same cost per square foot no matter what facility they lease for us.

Mr. Porter: Who is the current landlord of the property at 6003 Executive Blvd. Rockville?

Dr. Fauci: The landlord of the facility at 6003 Executive Boulevard is The Washington Science Center Joint Venture

Mr. Porter: Are you required to seek and receive Congressional approval of your leasing plans before proceeding?

Dr. Fauci: The Public Buildings Act of 1959, as amended by the Public Buildings Amendments of 1988, provided for the acquisition and administration of federally occupied space and includes a requirement for GSA to gain Congressional approval. In these amendments, the annual dollar threshold for Congressional approval of proposed leasing actions was raised from \$500,000 per annum in rent to \$1,500,000. The threshold is subject to an annual adjustment by the Administrator of General Services. The current threshold requiring Congressional approval is \$1,650,000. In fiscal year 1997 and 1998, the annual threshold will be \$1,740,000 and \$1,810,000, respectively.

EMERGING DISEASES

Mr. Bonilla: Dr. Fauci, you talked about emerging diseases in your opening statement. Would you tell us more about the threat these diseases pose to our country and the world? Would you also explain the role that the NIH plays versus that of the CDC?

Dr. Fauci: It is important to emphasize that infectious diseases have always posed and, as noted in the 1992 Institute of Medicine report on emerging infections, will continue to pose a substantial threat to human health both in the U.S. and worldwide. In this century, humankind has made great advances in science, medicine and public health, that caused a sense of complacency regarding our ability to deal with infectious diseases. This has changed more recently, due to epidemics such as AIDS and outbreaks such as Hanta and Ebola, that has enhanced public recognition that currently available drugs and vaccines will be increasingly inadequate to prevent and control infectious diseases in the future. This is true for several reasons, such as the capacity of microbes to change and adapt in ways that make them more virulent or resistant to drugs and vaccines; demographic and environmental changes that place man in situations where disease transmission is more likely to occur; and, increased international travel and trade that allow infections to spread rapidly and widely. These factors are making it ever easier for new or previously unrecognized infectious agents to emerge as human pathogens, and for known pathogens to re-emerge in regions where they were once under control. As illustrated by the AIDS epidemic, the threat these diseases pose is potentially enormous, both in humanitarian and economic terms.

The role of CDC in preparedness for emerging diseases focuses primarily on surveillance and detection of new threats. The role of NIH centers on research and research training. Research allows us to develop tools such as diagnostics, drugs, vaccines and other strategies to define, prevent and control the threat emerging infectious diseases. Training ensures that this country will maintain the expertise necessary to respond expeditiously to any future disease threat. CDC conducts research and training activities which are designed to integrate the laboratory science with epidemiology to optimize public health practice. We can only address the challenge of emerging diseases with an effective surveillance network linked to a vigorous and versatile research community that will continually refine our understanding of the biological basis of infectious diseases and create the best possible tools to respond and intervene.

AIDS CLINICAL TRIALS

Mr. Stokes: What is the status of the institute's most significant AIDS clinical Trials, specifically what can you tell us this year that you could not tell us last year? How much is included in the FY 1997 budget for AIDS Clinical Trials, and how does this compare to the funding levels for FY 1996, FY 1995 and FY 1994?

Dr. Fauci: NIAID-funded research has shown conclusively that substantial amounts of HIV are present from the earliest stages of infection and that viral levels and the degree of viral replication typically increase as HIV disease progresses. Scientists believe that they can delay or prevent HIV disease by suppressing viral replication. However, HIV quickly develops resistance to the currently available antiretroviral drugs. By using combinations of antiretrovirals, scientists hope to overcome the problems associated with the development of resistance. A central focus of NIAID AIDS research, therefore, is the development of safe, effective combination strategies that can suppress HIV for prolonged periods.

Recent trials have shown that combination regimens, treatments that employ two or more antiretroviral agents, are more effective than zidovudine (AZT) monotherapy, particularly early in disease. The first antiretroviral drug approved for treating HIV infection, AZT slows disease progression and prolongs life in patients with advanced HIV disease. When used alone, however, AZT does not provide a prolonged beneficial effect and patients quickly develop resistance to this drug. A study by NIAID's AIDS Clinical Trials Group (ACTG) found that didanosine (ddI), when used alone or in combination with AZT, and the combination of zalcitabine (ddC) and AZT were each significantly better than AZT alone in preventing disease progression and improving survival in patients with intermediate-stage HIV disease.

Protease inhibitors, a new class of anti-HIV compounds developed with the help of NIAID-funded basic research, have shown potent antiretroviral activity in preliminary studies. New studies have shown survival benefit and the reduction of the virus to undetected levels in patients on protease inhibitors in combination with other antiretrovirals. Several different pharmaceutical companies now have protease inhibitors in advanced stages of clinical development and are working with NIAID to investigate their use in acute infection, pediatric disease, and combination regimens.

Taken together, these studies are providing valuable information about the effectiveness of combination antiretroviral treatments over the course of disease and are providing significantly improved treatment options for patients.

Funding for NIAID AIDS Clinical Trials is as follows:

FY 1994 Actual	\$208,298,000
FY 1995 Actual	\$206,263,000
FY 1996 Estimate	\$211,453,000
FY 1997 Estimate	\$208,923,000

CHANGING FACES OF AIDS

Mr. Stokes: Doctor, as we have seen the faces of AIDS change with a shifting from gay males to a disease which disproportionately affects women and minorities. How are you addressing the changing faces of AIDS from a research, research training, and outreach standpoint? For each of these categories, provide a more detailed response for the record.

Dr. Fauci: The National Institute of Allergy and Infectious Diseases (NIAID) and the National Center for Research Resources (NCRR) cofund HIV/AIDS research projects of investigators at Research Centers at Minority Institutions (RCMI). RCMI's are predominantly minority institutions that offer the doctorate in the health professions and/or health related sciences. NIAID staff members take an active role in interacting with investigators, in making recommendations to applicants competing for funding, assisting with the pre-review of projects and yearly progress review. This has significantly enhanced the capacity of RCMI's for the conduct of biomedical and behavioral research. NIAID involvement has resulted in a dramatic increase in the quality and quantity of projects submitted and funded at minority institutions. RCMI investigators' ability to publish, have drugs tested, acquire patents and submit applications and secure peer reviewed funding has increased dramatically. The RCMI/NIAID portfolio now contains clinical, molecular, vaccine development, drug development, opportunistic infection and immunologic studies. NIAID's contribution to the cofunded projects is \$2,500,000 yearly. NCRR independently funds infrastructure for the conduct of HIV/AIDS research, as well as HIV/AIDS research projects.

NIAID recently collaborated with the NIH Office of Research on Minority Health (ORMH) to establish scientific collaborations between RCMI and Centers for AIDS Research (CFAR) investigators. Ten RCMI's currently are conducting HIV/AIDS research. The CFAR program of the NIAID and the National Institute of Mental Health (NIMH) provides administrative and research support to investigators to enhance and coordinate high quality AIDS and AIDS-related research projects. Twelve CFARs are currently conducting AIDS research nationwide. The NIAID/ORMH project will permit interaction of the RCMI investigators and scientists at all levels within the CFAR Program; establishment of collaborations with investigators at other institutions who are at the forefront of biomedical research; accessibility to a constantly increasing repertoire of current state-of-the-art technology; the opportunity to acquire preliminary data and subsequently apply for peer reviewed funding; and the possibility of publishing in peer reviewed journals.

In August 1995, we made six awards and the NCRR made an award in response to the Request for Applications entitled "Enhancement Awards for Under-represented Minority Researchers in HIV/AIDS." The RFA sought applications from under-represented minority investigators in both basic and clinical AIDS research. We made RO1 awards for a period of five years and included provisions for support of students/postdoctoral fellows as well as technicians. Each awardee also linked with experienced collaborators in HIV/AIDS or related research.

We also strive to more clearly define HIV disease in women through epidemiology research so that researchers can design clinical trials to address research questions of greatest therapeutic relevance to women. NIAID Epidemiology research is also examining the prevalence of high risk behavior (including commercial sex work and exchange of sex for drugs) and barriers to medical care among adolescents and women in order to design more effective risk reduction interventions. Other areas under investigation include: the effect of sexual transmission on clinical course; the pathogenesis of mechanisms of viral entry across genital mucosa, and the biological factors impeding or enhancing sexual transmission; the effect of concomitant HIV infection on common gynecologic conditions and infections; the effect of pregnancy on the course of HIV disease; and information on the efficacy of chemical or physical barrier methods in preventing transmission.

NIAID is studying how HIV disease in women may differ from that in men through two cohort studies, the Women's Interagency Health Study (WIHS) and the Women and Infants Transmission Study (WITS). The NIAID sponsored Women's Interagency HIV Study (WIHS) is a collaborative, multi-site, longitudinal study designed to investigate the impact of HIV infection on U.S. women. Awarded in August 1993, the study population will include approximately 2000 HIV-infected women and 500 HIV-uninfected women at high risk of acquiring HIV. This study is designed to: describe the spectrum and course of clinical manifestations of HIV infection in women; describe the pattern of immune markers in HIV-infected women; investigate factors that may delay or accelerate HIV-induced immune dysfunction and specific HIV-related conditions; and study the length of survival and quality of life of women living with HIV infection.

The NIAID sponsored Women and Infants Transmission Study that is being conducted in two phases examines HIV transmission during pregnancy or birth. WITS I enrolled three cohorts -- HIV-infected pregnant women, the offspring of HIV-infected pregnant women, and HIV-infected non-pregnant women. WITS II is recruiting only HIV-infected pregnant women and their offspring and follow all post-partum women and their children from both WITS I and WITS II until the end of the study. WITS II researchers are also examining factors related to HIV progression in women during pregnancy.

In addition, several clinical protocols are underway or planned to address woman-specific treatment research questions. These studies are conducted through three NIAID-supported clinical trials mechanisms: the AIDS Clinical Trials Group (ACTG), the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA), and the Division of AIDS Treatment Research Initiative (DATRI). Each of these programs is committed to ensuring the inclusion of HIV-infected women in trials, conducting research on HIV-associated conditions that specifically affect both non-pregnant and pregnant women, and identifying real or potential barriers that prevent the recruitment and retention of women to clinical trials

MINORITY RESEARCH

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your institute.

Dr. Fauci: In 1993 we fostered the creation of a "bridge" training initiative and targeted this program to minority scientists supported by the NIAID under the NIH Research Supplements to Underrepresented Minorities Program and minority scientists participating in training programs supported in our Intramural Research Program. We created this training initiative to facilitate the transition of junior investigators to that of independent researchers having collaborations with other researchers. We conduct this innovative program biannually and in FY 1995 we held our second "Bridging the Career Gap for Underrepresented Minority Scientists" and we were the host to fifty minority scientists. The program has outstanding minority and majority scientific leaders cover topics such as identifying career paths and the importance mentoring plays in navigating the waters of biomedical research. In addition, NIAID staff conducts an intensive workshop on NIH grantsmanship.

We are pleased to note that our innovative program is now being duplicated across the NIH. The National Heart Lung and Blood Institute conducted a similar program in the spring of 1995 and the National Institute of Arthritis and Metabolic Diseases is holding one in April of this year.

We are currently determining the successfulness of this program by identifying how many of our attendees have applied for NIH grants and received NIH grant support. We expect to have the results from our study by late summer.

We also have the Introduction to Biomedical Research Program (IBRP). We target this highly successful program to underrepresented minority students at the post secondary education levels of junior or senior and the first year of post baccalaureate education of graduate or medical school.

This program was initiated in FY 1979 to attract and retain minority students in careers in biomedical research and medicine and to date has served 852 students. Since the creation of this program, we have conducted one study to assess its impact on increasing the number of our students who remain in the sciences. The study looked at the first five years of the program (1979-1982), and a total of 188 participants. The attainment of a Ph.D., MD or MS was the benchmark used to ascertain success. From this cohort we learned that seven have earned Ph.D. degrees and that five of these individuals have applied for NIH grants; of the 188 participants, 117 have graduated from medical school and seven are currently enrolled in medical school; and that NIH had supported forty individuals in this cohort through training grants and fellowship awards. These findings have exceeded our expectations and we feel they have returned the investment made by the NIAID many times over.

Mr. Stokes: In most of the institutes, these programs are funded in Research Management and Support account, is this the case in your institute? If so, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are you hurting the most?

Dr. Fauci: We support our "Bridging the Career Gap for Underrepresented Minority Scientists" program, and other minority outreach efforts, with the Research Management and Support(RMS) account. The reduction to the RMS account in FY 1996 has created challenges in funding these programs. To conduct our "Bridging the Career Gap" program we entered into a collaboration with the NIH Office of Research on Minority Health in which they provided partial support for this activity. However, we had to curtail or eliminate staff attendance at meetings attracting scientific minority students and faculty. We use these meetings to heighten the attendees' awareness of our Institute's scientific agenda and career opportunities in biomedical research. In addition we use these sessions to acquaint participants with programs targeted to college students and junior researchers supported by NIAID.

To overcome this shortfall, we have depended heavily on the Internet to disseminate relevant information. We were the first of the NIH Institutes, and the 11th Federal agency to join, the Department of Energy's (DOE) Federal Information Exchange (FEDIX) homepage. This resource currently contains information on twelve Federal agencies with research and development initiatives. The DOE developed the FEDIX homepage to outreach more effectively to majority and minority educational institutions about their research and training programs and to provide information on employment opportunities. The National Science Foundation provided funding to insure that all Historically Black Colleges and Universities (HBCUs) and Hispanic-Serving Institutions (HSIs) were equipped with at least one computer dedicated to Internet usage through FEDIX. In addition, FEDIX supports a Minority On-line Information System to provide information on each HBCU's and HSI's faculty and programs to interested institutions and agencies. NIH joined the FEDIX homepage in mid-FY 1996, and several other Institutes are scheduled to join by the end of FY 1996.

Initially we used FEDIX to provide information on our Institute's research and training programs and employment opportunities, using its targeted audience and user friendly searching capabilities. We are now using FEDIX to launch an electronic information site for our Introduction to Biomedical Research and Summer Student Internship Programs.

MICROBICIDES

Mr. Stokes: In the past, you have emphasized the importance of the Institute's topical microbicides research effort and its implications for the prevention of sexually transmitted diseases. How much progress are we making developing safe and effective topical microbicides? How does the strategy used in the development of topical microbicides compare with that which researchers have applied to the development of vaccines?

Dr. Fauci: The strategy used in the development of topical microbicides is very similar to that used in the development of vaccines. It is based on three parallel tracks of research: basic science, product development, including *in vitro* products for antiviral HIV and HSV activity, and clinical evaluation, including behavioral research. We have established close ties with the commercial sector and community-based organizations are involved in the planning of clinical trials.

Our recent accomplishments in topical microbicides research includes:

1. We are currently conducting a Phase III clinical trial of a spermicidal film (N-9, VCF Apothicus). Results should be available in one year.
2. We completed a Phase II clinical trial on spermicidal gel (Advantage 24, Columbia Laboratories), and the FDA has approved an Investigational New Drug (IND) for Phase III.
3. We are beginning a Phase I trial for a new project, Acid Buffered Gel (ReproTech).
4. An IND has been submitted for a Phase II trial of lactobacillus suppository (Chrisope Technologies).
5. An IND is being prepared for safety and efficacy trials of Geda Plus (Geda Inc.).
6. We recently funded four topical microbicides program projects.

ASTHMA

Mr. Stokes: The subcommittee has heard testimony regarding the increasing number of deaths from asthma, to what is this attributed? What major initiatives are underway to address this critical health problem? How much is included in the FY 1997 budget for asthma research, and how does this compare with FY 1996, and FY 1995?

Dr. Fauci: Asthma deaths have risen steadily in the U.S. during the decade of the 1980's and this increase has continued through 1992, the last reporting period for which data are available. Surprisingly, this increase in mortality due to asthma is occurring at a time when some important risk factors for asthma such as smoking and air pollution have declined nationwide. The prevalence of asthma, and mortality due to asthma, are highest among disadvantaged people living in the poorest areas of our inner cities. Major factors contributing to the morbidity and mortality of asthma in this population include the failure to diagnose asthma early and suboptimal monitoring and treatment of many children with asthma. NIAID supports the National Cooperative Inner-City Asthma Study, a multi-site study to identify risk factors associated with childhood asthma in inner cities, and to study the effectiveness of a comprehensive intervention program. Very striking results are now surfacing from this study. Other major initiatives include over a dozen NIAID Demonstration and Education Research Projects to study asthma in minority communities. These projects are more limited in scope than the National

Cooperative Inner-City Asthma Study, are focused on different populations such as children in Head-Start or school-based programs, adults, and Southeast Asians, and are studying the effectiveness of different interventions.

In FY 1995, NIAID spent \$13,024,000 in asthma. We estimate spending \$13,545,000 and \$13,816,000 in FY 1996 and FY 1997 respectively.

Mr. Stokes: What major outreach activities are underway to address this public health problem?

Dr. Fauci: Major outreach activities include the National Cooperative Inner-City Asthma Study and NIAID's many Demonstration and Education Research Projects. NIAID supports Demonstration and Education Research Projects at fourteen of the NIAID extramural Asthma, Allergic, and Immunologic Diseases Cooperative Research Centers. Investigators at these sites are testing various educational interventions to improve asthma knowledge and self-management skills, or are evaluating the impact of environmental interventions to eliminate or diminish exposure to indoor allergens. We have established additional Demonstration and Education Research Projects at university and clinic sites in Atlanta, Boston, Miami, Dallas, and San Diego. Researchers at these sites are evaluating school-based and clinic-based educational interventions. At one of these sites, researchers are developing interactive video games as educational tools for inner-city children. At two of these sites researchers are developing computer-based clinical management algorithms designed for inner-city health care providers.

Mr. Stokes: Doctor, asthma ranks second among the chronic health problems most frequently reported by African Americans, especially those less than eighteen years of age.

Mr. Stokes: Would you bring us up-to-date on programs underway at the institute that are designed to address this serious health problem in at-risk populations, how much is included in your budget to address asthma in African Americans and other minority at-risk populations? How much of that amount is for asthma education and outreach, and how much is for asthma research and research training?

Dr. Fauci: Approximately 75 percent of the children enrolled in the National Cooperative Inner-City Asthma Study were African Americans and 20 percent were Hispanic. We similarly focus NIAID Demonstration and Education Research Projects on minority populations. Most of these projects are directed at largely African-American and Hispanic communities; however, several focus on narrower population groups such as individuals in predominantly Cuban-American, Puerto Rican, and Southeast Asian communities. In FY 1995, we invested \$3,673,460 in the National Inner-City Asthma Study and \$3,215,000 in Demonstration and Education Research Projects in minority and at-risk populations.

In FY 1996 we renewed the National Inner-City Asthma Study. We intend this renewal to extend on the promising results of the first study. We will develop and test additional interventions to promote patient and physician education, and to diminish

environmental factors that contribute to asthma severity. We are requesting \$2,340,000 in FY 1997 for this study. We have entered into a collaborative effort with the NIEHS in and they will contribute \$780,000 toward the funding of this study in FY 1997.

ASTHMA AND THE ENVIRONMENT

Mr. Stokes: Doctor, last year you indicated that recent phase-I studies revealed that African Americans and Hispanics living in inner-city areas have unusually high rates of asthma morbidity and mortality. Are we making any measurable progress in this research area? To what extent is the asthma health problem related to environmental health?

Dr. Fauci: We are making very meaningful progress in the National Cooperative Inner-City Asthma Study. We designed the first phase of the National Cooperative Inner-City Asthma Study to identify factors associated with severity of asthma in children age 4-11. The second phase, completed in February 1996, studied the effectiveness of a comprehensive program to develop improved knowledge about asthma, to promote better asthma self-management skills, and to eliminate or decrease exposure to environmental factors associated with increased morbidity from asthma. Some very promising findings are now emerging from both phases of this study.

Phase I enrolled 1,528 children, with 92 percent participation maintained throughout the study. This represents an exceptionally high recruitment and retention of subjects in a longitudinal study of this type. Involvement of the community and strategies to enhance patient self-management contributed importantly to the retention of participants. Factors associated with asthma severity included: exposure to high levels of indoor allergens, especially cockroach allergen; high levels of tobacco smoking among family members and caretakers; exposure to high levels of nitrogen dioxide, a respiratory irritant, that was found in approximately 25 percent of homes.

We enrolled more than 1,000 children in phase II of the study. While the results are still preliminary, children in the intervention limb of the study had striking reductions, approximately 30 percent, in major symptoms, in school absenteeism, in hospitalizations, and in emergency room visits for asthma.

The relationship between asthma and the environment has received much attention in the public media. An international workshop on "Asthma and the Environment" sponsored by EPA, NIAID, NHLBI, NIEHS, CDC, and NIOSH was held in May 1996. Although very few carefully controlled longitudinal studies have been published, there was general agreement among the workshop participants that outdoor air pollution, including exposure to ozone, diesel exhaust, and airborne particulate matter, most likely does not *cause* asthma, but may contribute to the *exacerbation* of existing asthma. In contrast, sensitization to indoor allergens, including dust mite, cockroach, fungal, mouse, rat, and cat allergens, is a necessary step in the development of allergic asthma. Findings of the National Cooperative Inner-City Asthma Study suggest that exposure to some of these allergens contributes to the prevalence and severity of asthma in the inner-city environment.

Mr. Stokes: Which areas of basic research have provided the most knowledge on this disease? How much is included in the budget request for each of these areas, compared to FY 1996 and FY 1995?

Dr. Fauci: We increasingly recognize chronic inflammation of the airways as a major factor in the pathogenesis of asthma. NIAID supports basic research on the recruitment of inflammatory cells to the lungs and on the mechanisms through which they cause airway inflammation. We have recently developed animal models that more closely mimic the immunological and physiological abnormalities in human asthma. We are using the tools of molecular biology to develop transgenic and gene "knockout" models that can test the roles of specific cells and mediators in the pathogenesis of asthma. The knowledge gained from these studies has contributed to wider use of anti-inflammatory agents as a safer and more effective approach to the management of asthma.

Another important area of basic research is the identification and structural characterization of environmental allergens. Other investigators are identifying the mechanisms that regulate production of IgE antibodies, the class of antibody molecules that mediate allergic reactions. Finally, NIAID-supported investigators are searching for genes that determine an individual's susceptibility to allergic disorders, including asthma.

CLINICAL TRIALS

Mr. Stokes: What are some of your most significant clinical trials, and specifically what can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Fauci: The following describes some of our most significant clinical trials:

Asthma. The first phase of the National Cooperative Inner-City Asthma Study (1991-1994) was designed to identify factors associated with severity of asthma in children age 4-11. The second phase, completed in February 1996, studied the effectiveness of a comprehensive program to develop improved knowledge about asthma, to promote better asthma self-management skills, and to eliminate or decrease exposure to environmental factors associated with increased morbidity from asthma. Some very promising findings are now emerging from both phases of this study.

Phase I enrolled 1,528 children, with 92 percent participation maintained throughout the study. This represents an exceptionally high recruitment and retention of subjects in a longitudinal study of this type. Involvement of the community and strategies to enhance patient self-management contributed importantly to the retention of participants. Factors that were associated with asthma severity included: exposure to high levels of indoor allergens, especially cockroach allergen; high levels of tobacco smoking among family members and caretakers; exposure to high levels of nitrogen dioxide, a respiratory irritant, that was found in ~25 percent of homes. Over half of the participants found it difficult to get follow-up care for their asthma.

Over 1000 children were enrolled in phase II of the study. While the results are still preliminary, children in the intervention limb of the study had striking reductions (~30 percent) in major symptoms, in school absenteeism, in hospitalizations, and in emergency room visits for asthma.

Kidney Transplantation. The NIAID-supported Cooperative Clinical Trial in Adult Kidney Transplantation has been a leader in setting new models for the conduct of clinical trials in transplantation. This past year, the cooperative study has demonstrated that infusion of blood from the organ donor prior to transplantation has a significant positive effect on long-term graft survival. This same treatment allows some patients to be able to discontinue steroid therapy usually necessary to help prevent graft rejection and therefore, avoid the toxic side effects of this drug.

These trials, for the first time, standardize the criteria used to grade this type of rejection and is in its final stage. This set of criteria will help pathologists worldwide to standardize the type of rejection and, therefore, allow clinicians to more knowledgeably treat the transplant recipient to prevent loss of the graft, leading to improved health for transplant recipients.

Combination Therapy for HIV. Recent trials have shown that combination regimens, treatments that employ two or more antiretroviral agents, are more effective than zidovudine (AZT) monotherapy, particularly early in disease. The first antiretroviral drug approved for treating HIV infection, AZT slows disease progression and prolongs life in patients with advanced HIV disease. When used alone, however, AZT does not provide a prolonged beneficial effect and patients quickly develop resistance to this drug. A study by NIAID's AIDS Clinical Trials Group (ACTG) found that didanosine (ddI), when used alone or in combination with AZT, and the combination of zalcitabine (ddC) and AZT were each significantly better than AZT alone in preventing disease progression and improving survival in patients with intermediate-stage HIV disease.

Protease inhibitors. Protease inhibitors, a new class of anti-HIV compounds developed with the help of NIAID-funded basic research, have shown potent antiretroviral activity in preliminary studies. New studies have shown survival benefit and the reduction of the virus to undetected levels in patients on protease inhibitors in combination with other antiretrovirals. Several different pharmaceutical companies now have protease inhibitors in advanced stages of clinical development and are working with NIAID to investigate their use in acute infection, pediatric disease, and combination regimens.

Pertussis. Over the past year, two large NIAID-supported efficacy trials of acellular pertussis vaccines in Sweden and Italy were successfully completed. The trial results demonstrated the excellent safety and efficacy of three acellular pertussis vaccines when compared to a whole cell pertussis vaccine in randomized, double blinded, placebo-controlled trials. Acellular pertussis vaccines are being evaluated for licensure by the FDA for use in babies in the United States.

Maternal immunization. Maternal immunization has the potential to enhance the passive immunity of infants against agents that produce life-threatening illnesses in early childhood. In some instances, immunization during pregnancy will provide important protection for the mother as well. The NIAID Maternal Immunization Program is currently supporting several clinical trials with the potential for significant public health impact. A study that enrolled 519 American Indian women in Arizona was recently completed. These women received either a Hib conjugate vaccine or a pneumococcal polysaccharide vaccine prior to becoming pregnant. The newborns of these women were monitored for antibody transfer from their mothers, and the trial demonstrated that immunization of childbearing-aged women can increase protective antibody levels in offspring infants.

In a series of small and inter-related clinical trials in over 300 child-bearing aged women, four different investigational group B streptococcal (GBS) conjugate vaccines have recently been evaluated for safety and immunogenicity. During the last two decades, GBS has emerged as a major infectious cause of perinatal morbidity and neonatal mortality. Infants acquire the disease in utero or during birth and maternal immunization has the potential to provide protection to newborn infants. All of the investigational vaccines were safe and immunogenic and the goal is to now move forward to a study in which women will be immunized in the third trimester of pregnancy.

CLINICAL TRIALS

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Fauci: NIAID funding for clinical trials is as follows:

FY 1994 Actual	\$258,507,000
FY 1995 Actual	\$251,643,000
FY 1996 Estimate	\$258,649,000
FY 1997 Estimate	\$257,063,000

Mr. Stokes: What is the institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Fauci: We are actively engaged in exploring how to attract women and minorities to our studies and have an extensive outreach program to encourage minorities to participate in our clinical studies. NIAID and the AIDS Clinical Trials Information Service provided exhibits and materials for many national and regional meetings focusing on concerns of minority populations, including the 10th Biennial National Conference on Hispanic Health and Human Services; conferences sponsored by La Raza, Blacks in Government, the National Association of Community Health Centers,

the National Minority AIDS Council, and the Congressional Black Caucus/Health Braintrust; and several meetings in Puerto Rico sponsored by the Health Resources and Services Administration, among others.

The inclusion of women in our AIDS clinical trials has increased steadily since 1988. Currently, women represent 14 percent of the patients on study in AIDS therapeutic clinical trials. The current percentage of women on study in the ACTG is 10 percent; the CPCRA is 21 percent and DATRI is 11 percent. Women make up 44 percent of the patients currently on study for the AIDS Vaccine Evaluation Group. This trend is reflective of the history of the epidemic in women which began expanding in women in the mid-1980's. The current enrollment of people of minority background in NIAID-supported therapeutic clinical trials is 52 percent for the ACTG, 60 percent for the CPCRA, and 11 percent for the DATRI.

In FY 1996 we recompeted the Adult ACTG. One of the criteria for this recompetition was to ensure the enrollment of a proportionate number of minorities at the sites. Additionally, within \$67 million budget for the Adult ACTG, the NIAID set aside \$3.5 million exclusively for minority institutions.

Several initiatives have been designed to more clearly define HIV disease in women through epidemiologic research so that researchers can design clinical trials to address research questions of greatest therapeutic relevance to women. In 1993, the PHS multi-agency sponsored Women's Interagency HIV Study (WIHS), of which NIAID is a sponsor, was initiated. The WIHS is a collaborative, multi-site, longitudinal study designed to investigate the impact of HIV infection on women. The study population, once enrollment is complete, will include approximately 2,000 HIV-infected women and 500 HIV-infected females at high risk of acquiring HIV who are aged 13 years or older at the time of enrollment.

The NIAID-sponsored Women and Infants Transmission Study (WITS I/II) examines factors related to HIV transmission during pregnancy or birth as well as the progression of the disease in women during pregnancy. WITS is being conducted in five cities: Chicago, Boston, Puerto Rico, New York City and Houston.

Our Urban Asthma Study is targeted to minority children suffering from asthma and residing in urban centers. Data collection for phase I of the National Cooperative Inner-City Asthma Study (NCICAS) was completed in 1994. This ongoing multicenter study explores the factors that contribute to the increasing rates of morbidity and mortality among inner-city African American and Hispanic/Latino children. Phase I resulted in the development of culturally appropriate questionnaires to measure asthma morbidity and compliance with asthma therapy, procedures to measure allergen levels, and a coding scheme to evaluate doctor-patient communication.

Phase II of the NCICAS has begun and includes interventions to reduce allergen levels, assignment of asthma counselors to inner-city families to empower them to make better use of the medical care system, facilitation of asthma treatment and access to care, and education of patients on self-management skills.

In FY 1991, the NIAID launched the first NIH cooperative clinical trial in kidney transplantation, a multicenter prospective study designed to translate some of the most recent developments of basic research into new immunosuppressive modalities to prevent kidney graft rejection. A network of transplantation centers throughout the United States is evaluating new immunosuppressive agents as they become available. Efforts were made and have been successful at recruiting women for this trial. Women, as a result of them bearing children, develop antibodies directed against the human leukocyte antigens inherited from the father, which in turn, reduces their chances for compatibility with an organ donor. While these antibodies can be present due to other causes, such as transfusions, and can be present in men, high titers of these antibodies occur more frequently in women.

Mr. Stokes: How critical is gene therapy research to furthering advances in areas of research which are under the purview of your institute? What diseases and disorders would benefit from enhanced research in this area?

Dr. Fauci: Gene therapy is based on the manipulation of genetic material in an individual for the treatment of a specific disease. This can involve: 1) gene replacement to restore a non-functional gene; 2) gene inactivation such as the destruction of deleterious genetic information such as that of HIV-1 RNA in infected cells; and 3) gene repair such as the correction of a mutant gene inside a cell as in the case of sickle cell anemia. Gene therapy requires the use of a mechanism or vector to deliver the genetic information to the patient. This can be achieved either by using defective viruses or non-viral particles to carry the genetic material directly to blood or tissues, or indirectly, by introducing modified cells that have foreign genetic material as the therapeutic agent.

In the specific case of HIV-1 infection, gene therapy offers the possibility to protect critical immune cells such as CD4 helper cells against the damaging effect of virus replication. In so doing, it is anticipated that the patient's functional immune system could be preserved.

While the potential of gene therapy for the treatment of human disease is unrefuted, significant practical problems and scientific challenges remain. The future success of gene therapy will depend on a more profound understanding of the pathophysiology of the disease being treated. That knowledge is critical, not only for the improved design of gene therapy strategies, but also for more effective pharmacological approaches for managing the disease. Significant advances must also be made in the scientific areas that constitute the field of gene therapy, including virology, cell biology, immunology, molecular biology. It will also be essential to develop new and improved vectors to target delivery to specific cells or tissue, to sustain long-term expression of the therapeutic gene, and to maintain regulated expression of the gene in a way that simulates the natural state.

Recognizing the potential of gene therapy for the future treatment of HIV disease, NIAID is integrating extensive studies on HIV pathophysiology and immunology with basic studies on gene therapy. Information gained will be used to evaluate these findings in surrogate animal models, including monkeys infected with the simian homologue of

HIV. In addition, carefully designed pilot clinical studies in a small number of patients are used to further advance the basic and clinical knowledge. Information gained from this coordinated and comprehensive approach is used in an iterative fashion to build upon and further improve upon gene therapy approaches. Several studies conducted by NIAID scientists or NIAID grantees have provided fundamental information that have paved the way to subsequent studies and added to the knowledge base of HIV pathophysiology.

Mr. Stokes: I understand that individuals with HIV-2 appear to have some protective mechanism against becoming infected with HIV-1. How close are we to understanding and unraveling this critical difference between the two forms of HIV? What major work is underway here in the U.S. to study these differences?

Dr. Fauci: Protection from infection with HIV-1 after an initial HIV-2 infection does not imply that there are critical differences between the two forms of HIV. It only suggests that the primary infection causes a change in the host that results in the blockage of infection with, or reduction of replication of the second related virus. This could be due to either an immunological response mounted by the host to the primary infection, or some non-immunological phenomenon. One study carried out in West Africa, one of the few sites in the world where both HIV-1 and HIV-2 are endemic, suggested that prior infection with HIV-2 reduced the risk of infection with HIV-1. The results of this study were far from conclusive, since the numbers of individuals studied was extremely small. Based on the results, it has been suggested that HIV-2 may be used for the development of a vaccine against HIV-1, but since HIV-2 also causes disease, the utility of a live HIV-2-based vaccine is questionable.

To verify the reported results, larger, better controlled studies would need to be carried out. To unravel the mechanism of protection, if indeed verified by these in-depth studies, would require intensive immunological and biological analyses. Under NIH funding, a large cohort of HIV-negative individuals is being assembled in the West African country of Senegal in preparation for future AIDS prevention studies, and such a cohort could be used to investigate this potential protective phenomenon, but no such study is currently planned. Studies carried out by the Centers for Disease and Prevention have indicated that many individuals in West Africa are indeed dually infected with both HIV-1 and HIV-2, showing that any protection offered by infection with one HIV type against the other is not complete.

A University of Maryland study recently reported that HIV-2 inhibits the replication of HIV-1 at the molecular level, indicating that non-immunological mechanisms may also play a role in any possible protective mechanism. These results may have implications for gene therapy against AIDS.

Chimpanzee studies are currently underway to determine whether infection with one strain of HIV-1 can protect against infection with another HIV-1 strain. While these studies are incomplete, initial results suggest that protection is seen when the two strains tested are closely related but no protection is observed when testing two different genetic subtypes of HIV-1. While similar chimpanzee experiments have not been carried

out testing HIV-2 protection against HIV-1 infection, the results from the previous HIV-1 studies, coupled with the known genetic differences between HIV-1 and HIV-2, would suggest that protection would most likely not be observed.

MICROBICIDE RESEARCH

Ms. Lowey: Please give us an update on the status of clinical trials for over-the-counter spermicides as microbicides and for new topical microbicide products?

Dr. Fauci: The following is a status of our clinical trial efforts in topical microbicides:

1. We are currently conducting a Phase III clinical trial of a spermicidal film (N-9, VCF Apothicus). Results should be available in one year
2. We completed a Phase II clinical trial on spermicidal gel (Advantage 24, Columbia Laboratories), and the FDA has approved an Investigational New Drug (IND) for Phase III.
3. We are beginning a Phase I trial for a new project, Acid Buffered Gel (ReproTech).
4. An IND has been submitted for a Phase II trial of lactobacillus suppository (Chrisope Technologies).
5. An IND is being prepared for safety and efficacy trials of Geda Plus (Geda Inc.).

Ms. Lowey: Please explain NIH's relationship with industry in terms of topical microbicide product development efforts. Are there obstacles to engaging in effective collaborations with the commercial sector in this effort?

Dr. Fauci: NIAID staff have been pro-active in contacting commercial representatives about new and existing products in various stages of development. In the last year over a dozen companies have expressed interest in collaborating on some aspect of product development and/or evaluation. We are working to provide guidance and assistance in pre-clinical and clinical testing. Commercial collaborators are involved in two of the three recently awarded topical microbicide program projects. Finally NIAID is working with the FDA to clarify relevant regulatory requirements. This will be of great value as we move forward with commercial partners to evaluate topical microbicides in clinical trials.

Ms. Lowey: What are the plans for the growth of the topical microbicide research program, given the limitation of resources?

Dr. Fauci: Topical microbicides will continue to be a high priority for the institute and we anticipate maintaining our commitment to research in this area. Furthermore, we have and will continue to use existing infrastructure for the development and evaluation of these products. For example, use of international clinical trials infrastructure is a cost effective way to evaluate topical microbicides while providing an opportunity to assess feasibility of these products to prevent and control STDs/HIV in the developing world.

Ms. Lowey: In order to deliver safe, effective topical microbicides in a timely fashion, clinical trials evaluating the safety and efficacy of topical microbicides must be given a higher priority. Please explain existing capacity for these trials; in your opinion, is it adequate to accommodate the needs and opportunities for fast track development of these products?

Dr. Fauci: We are currently utilizing the Division of AIDS HIVNET Network for Prevention Trials infrastructure as well as the Vaccine Treatment and Evaluation Units infrastructure to carry out our topical microbicide research efforts.

In order to fast track any product development effort, infrastructure, staff, resources, and appropriate populations are required. In a time of resource limitations, a deficiency in any of these areas could hinder product development. We will continue to give this product development effort a high priority.

LYME DISEASE

Ms. Lowey: Please provide an update on the status of NIAID's Lyme disease research. In the past year, how has the Institute contributed to the important search to prevent and treat lyme disease? What are the Institute's priorities for Lyme disease research in the coming year?

Dr. Fauci: The NIAID funds 44 grants and 2 contracts that, largely through the use of well-defined experimental models, have provided new information and valuable insights on: [a] how borreliosis is transmitted to humans by infected ticks; [b] molecular aspects associated with pathogenesis and damage to host tissues; [c] the host's immune response to *Borrelia*; [d] mechanisms involved in the development of protective immunity; [e] and the characterization of *Borrelia* antigens, suitable for use in vaccines. We now know that: an infected tick must be attached to a human host for at least 48-72 hours before being able to transmit an infection; antibodies specific for the OspA antigen of *Borrelia* are able to kill *Borrelia* directly in the midgut of ticks, but not in humans after *Borrelia* have established an infection; and, the surface antigens of *Borrelia* are potent immunomodulators and, by stimulating the release of various cytokines, may be responsible for inducing the inflammatory, as well as rheumatological and neurological symptoms characteristic of Lyme disease.

In its early stages, Lyme disease is easily treated with a short course of oral antibiotics. However, there is much controversy as to whether antibiotic therapy is effective in treating patients with chronic Lyme disease, in which there is an array of debilitating neurological symptoms. Accordingly, we are supporting several efforts related to chronic Lyme disease. For example, we are funding a grant that is conducting a placebo-controlled clinical study to examine the efficacy of prolonged ceftriaxone therapy for the treatment of this condition. Early this summer, we will award a contract to conduct similar clinical studies using other antibiotics to obtain conclusive information on the effectiveness of such therapies, as well as the appropriate antibiotics and regimens to be used in such approaches. In addition, researchers in NIAID's intramural program

have recently initiated clinical studies to characterize chronic Lyme disease more completely so that rational and more effective therapeutic approaches can be devised.

In addition, efforts to develop more sensitive and specific diagnostic tests, and efforts related to the development of vaccines, continue to represent a major portion of the Institute's Lyme disease portfolio.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

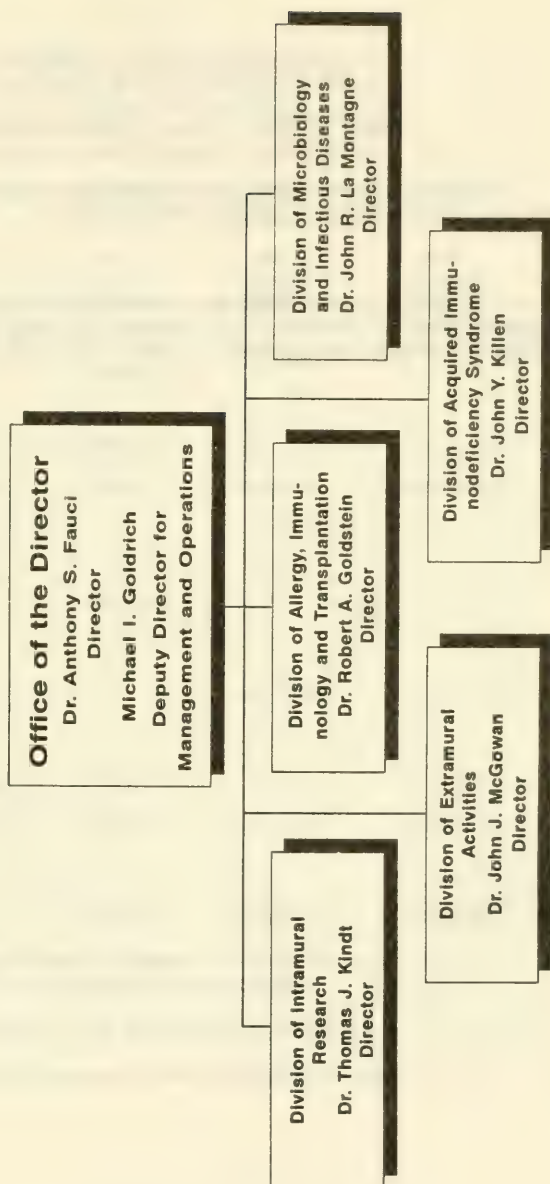
National Institute of Allergy and Infectious Diseases

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National Institutes of Health

National Institute of Allergy and Infectious Diseases

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, \$584,362,000.

Note: A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on levels provided in three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$536,416,000	\$1,169,628,000	\$584,362,000
Reduction in accordance with P.L. 103-333.....	-569,000		
Rescission in accordance with P.L. 104-19.....	-648,000		
Subtotal, Adjusted Appropriation.....	535,199,000	1,169,628,000	584,362,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-458,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....		-596,018,000	
Comparative transfer from: Other NIH Institutes for Management Fund adjustment.....	2,199,000		
Subtotal, adjusted budget authority....	536,940,000	573,610,000	584,362,000
Unobligated balance lapsing.....	—	—	—
Total Obligations.....	536,940,000	573,610,000	584,362,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1995—\$18,316,000; FY 1996—\$20,000,000; FY 1997—\$22,000,000.

Excludes funding for HIV activities: FY 1995—\$557,766,000; FY 1997—\$624,368,000.

Note: Excludes \$2,694,000 for royalties received in FY 1995 and \$3,000,000 in FY 1996.

Justification**National Institute of Allergy and Infectious Diseases**

FY 1995 Actual		FY 1996 Appropriation		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
1,042	\$536,940,000	1,048	\$573,610,000	1,048	\$584,362,000	--	+\$10,752,000

General Statement

Research supported by the National Institute of Allergy and Infectious Diseases (NIAID) continues to decrease or eliminate the burden of allergic and infectious diseases. The NIAID supports diagnostic, drug, and vaccine development that reduces the Nation's health care costs. These efforts have significantly benefitted the health of Americans, in particular, and they hold great potential for the developing world. Challenges abound, however, as we encounter new and re-emerging problems, such as acquired immune deficiency syndrome (AIDS), chronic fatigue syndrome (CFS), Lyme disease, ebola hemorrhagic fever, hantavirus pulmonary syndrome and other emerging microbes. Other diseases, such as tuberculosis (TB), enterococcal infections and pneumococcal pneumonia are increasingly problematic because of the development of resistance to currently available drugs. In addition, allergic diseases, including asthma, are currently among the major causes of illness and disability in the United States, affecting as many as forty million Americans. These diseases result in considerable morbidity, mortality, pain and suffering; they result in absenteeism from work or school; consequently, they contribute to high medical care costs. The NIAID diligently strives to develop better ways to diagnose, treat, and prevent these illnesses.

We cannot overemphasize the intrinsic value of basic research in our quest for research results that have immediate application to persons afflicted with disease. Basic research is the key to developing public health tools. Basic science has contributed to the dramatic growth in our understanding of disease and diseases processes and is essential to discovering new treatment and prevention strategies. The information gleaned from fundamental research provides the basis for fashioning clinical and biological interventions; thus, we believe that investments in NIAID research will ultimately result in improved health and quality of life by improving the diagnosis, treatment, and prevention of diseases.

This document provides justification for the FY 1997 non-AIDS activities of the National Institute of Allergy and Infectious Diseases. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The President's budget request of \$584,362,000 for the NIAID represents current law requirements.

Funding for the NIAID non-AIDS research program during the last five years has been as follows:

	<u>Amount</u>	<u>FTE</u>
FY 1992	511,142,000	1,091
FY 1993	524,529,000	1,136
FY 1994	522,857,000	1,102
FY 1995	536,940,000	1,042
FY 1996	573,610,000	1,048

Program Purpose and Method of Operation

Infectious diseases remain the most common cause of death for children worldwide, and disorders of the immune system afflict more than one in ten Americans. NIAID-supported biomedical research has advanced the prevention and treatment of diseases to individuals and society. These advances reduce suffering and save lives, and they translate into economic cost savings by reducing the use of health care services and improving human productivity. The NIAID's mission is to conduct and support research and training aimed at alleviating this suffering caused by illnesses.

To accomplish this mission, NIAID supports research and training grants and contracts at many universities and medical centers in the United States. The Institute also conducts basic and clinical investigations in its intramural laboratories at Bethesda, Rockville, and Frederick, Maryland, and at Hamilton, Montana. The NIAID has four major research divisions: Allergy, Immunology, and Transplantation; Acquired Immunodeficiency Syndrome; Microbiology and Infectious Diseases, and Intramural Research.

Overall Budget Policy

The NIAID FY 1997 budget request for non-AIDS research is \$584,362,000, an increase of \$10,752,000 or 1.9 percent over the comparable FY 1996 level of \$573,610,000. This request includes an increase of \$3,000,000 targeted to new approaches to pathogenesis and \$2,000,000 targeted to new preventive strategies against disease. The FY 1997 request will support 1,694 research project grants at \$397,101,000 an increase of 29 awards and \$10,765,000 over the FY 1996 comparable amount. This budget was developed according to the principles of the NIH Cost Management Plan. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical

Research and Development Price Index. Thus, in FY 1997, noncompeting research project grants will receive an average increase of 2 percent over the FY 1996 direct cost level for recurring items of expense. The average cost of competing research project grants will also increase by 2 percent. These levels will maintain stability of support within the extramural grant community while providing new research opportunities.

Economic & Public Health Benefits of NIAID Research

Research Advances that Improve Public Health

NIAID-supported research results in prevention of disease, prevention of premature death, decreased hospitalization, improved quality of life, improved work productivity, and decreased absenteeism from work and school. NIAID research in infectious diseases and immune system disorders focuses on diseases that exact a heavy toll on Americans and on our health care system. Many of these diseases disproportionately affect minorities, women, and children. Enormous human and economic benefits result from preventing, curing, or controlling these diseases through the development and use of vaccines, diagnostic tests, and drug therapies. Additionally, research on rare diseases often leads to "spinoffs" and advances in the treatment and prevention of diseases that have considerable economic burden. Treating or preventing illness can prevent premature death and disease-related disability, resulting in a long healthy life and reducing the economic burden of disease. Treatments and cures for chronic illnesses increase productivity and reduce the use of health care services. While measuring directly the economic impact of basic research is difficult, recognizing that basic research is key to the development of public health tools is important. Basic science has contributed to the dramatic growth in our understanding of disease and disease processes, which is essential to discovering new treatment and prevention strategies. The following are some examples of the benefits derived from NIAID-funded research:

Haemophilus influenzae (Hib) type b polysaccharide vaccine can eliminate Hib disease: NIAID-supported investigators helped develop two generations of Hib type b polysaccharide vaccines, which have virtually eliminated serious invasive Hib disease in the United States. Since 1988, when the new conjugate Hib vaccines became available in the United States, there was a 95 percent reduction in the incidences of the disease among children under the age of five. Before these vaccines, Hib was the leading cause of pediatric bacterial meningitis in the United States, affecting 10,000 to 15,000 infants per year. Hib was also the cause of a wide spectrum of other serious infections in children. We now include Hib disease in the list of vaccine-preventable diseases targeted for elimination in the United States by 1996. NIAID's investment in this research was \$20.1 million; we conservatively estimate that the Hib vaccine saved more than \$400 million per year.

Pertussis vaccine trials demonstrate that acellular pertussis vaccines have fewer side effects than the current vaccine: Pertussis, also known as whooping cough, is responsible for an estimated 350,000 deaths annually worldwide, primarily among infants. A vaccine made from whole, killed *Bordetella pertussis* organisms has been in use for nearly fifty years and has been extremely effective in controlling whooping cough in the United States. The whole-cell vaccine, however, has been associated with adverse side effects more frequently than other vaccines

usually used for infants. Concerns among the public about side effects associated with these products have resulted in a decrease in their use in many parts of the world. The decline in pertussis immunization in previously well-vaccinated populations has resulted in substantial pertussis epidemics. The results from these recent clinical trials mark important progress toward the eventual goal of developing combination vaccines that can protect children worldwide against many diseases with a minimum of vaccine shots and a minimum of side effects.

Vaccine to prevent chickenpox licensed: More than 3.7 million cases of chickenpox occur in the U.S. annually, with 90 percent of cases in children less than fifteen years of age. We estimate the economic cost at \$400 million annually, primarily in lost wages by parents. Researchers in Japan developed the first chickenpox vaccine in 1974 and tested it in healthy and leukemic children there. Subsequently, an NIAID sponsored clinical trial proved that we could successfully vaccinate leukemic children with the vaccine, but that we must administer cautiously and under control vaccination circumstances. The safety and efficacy of the vaccine in the leukemic children provided impetus for the development of the current vaccine. In March 1995, the FDA approved a vaccine to prevent chickenpox. NIAID supported researchers continue to investigate the basis of protective immunity, its apparent waning with age, and the basis of virus latency and reactivation. We will need such knowledge to follow vaccines and to understand risk factors for zoster.

Rotavirus vaccine protects against severe diarrhea in children: In developing countries each year, rotaviruses, the most common cause of severe diarrhea, affect more than eighteen million infants and children less than five years of age and cause an estimated 870,000 deaths worldwide. NIAID intramural investigators developed and patented two rotavirus strains for use in vaccines against rotavirus. Researchers designed the vaccines by substituting a gene from a human rotavirus strain for one in a weakened rotavirus that infects rhesus monkeys. The gene has instructions to make a protein on the virus' surface, where the immune system can easily recognize it and then tailor-make antibodies to fight that viral strain. Clinical trials in infants showed that vaccination with both vaccines was safe and significantly reduced the incidence of rotavirus diarrhea, reducing medical visits by 67 to 78 percent. In a multicenter trial, the vaccine was 80 percent protective against severe rotaviral disease and 100 percent effective in preventing dehydrating illness. In the United States, rotaviruses cause more than 3.5 million episodes of gastroenteritis, one million of which are severe; 500,000 doctor visits; 70,000 to 100,000 hospitalizations at a direct cost of \$500 million; and 75-125 deaths in infants and young children every year. An effective vaccine could prevent more than one million cases of severe rotaviral diarrhea and 65,000 hospitalizations in children less than five years of age in the United States annually.

Acyclovir treatment for neonatal herpes: NIAID-funded investigators showed that acyclovir is an effective therapy for treating neonatal herpes, a severe infection that can lead to death and permanent neurologic damage in newborns of women with genital herpes simplex infections. NIAID invested \$5.1 million in research support; acyclovir therapy for neonatal herpes can save an estimated \$184 million in reduced lifetime treatment costs and lost earnings for a one-year cohort of infected infants.

Diagnostic test for chlamydia infection allows early treatment, which prevents pelvic inflammatory disease (PID): Chlamydial infection is the most common bacterial sexually transmitted disease in the United States, with about four million new cases each year and an annual cost exceeding \$2 billion. Untreated chlamydial infection can lead to PID and long-term consequences such as infertility and tubal pregnancy; however, as many as 70 percent of women with chlamydial infections have no symptoms and do not seek treatment. A NIAID-supported clinical study showed that women whom we screened and treated for asymptomatic chlamydial infections had a 50 percent lower incidence of PID than women whom we treated after they showed signs of disease. NIAID intramural scientists have developed a highly sensitive and non-invasive urine assay that allows earlier detection of both asymptomatic and symptomatic cases of this disease. If widely used, the assay could detect early chlamydial infections and prevent the infection's adverse consequences.

New diagnostic assays for rapid identification of tuberculosis (TB): Multi-drug resistant strains of *Mycobacterium tuberculosis* have recently emerged and caused serious outbreaks of disease. Current diagnostic tests to identify infected patients and to decide which drugs to use takes several weeks before results are available, during which time the patient may be receiving drugs that are not effective and may transmit the disease to others. Two NIAID-supported investigators have developed techniques for rapidly identifying TB and determining the drug susceptibility of TB isolates. The first assay is based on polymerase chain reaction (PCR) technology, which enables the amplification of very small amounts of DNA. In this assay, we use PCR to identify TB directly from clinical specimens. The other assay uses the enzyme luciferase to detect the drug susceptibility patterns of the isolates. Not only is this a rapid and sensitive method for detecting resistant TB strains, but because of its potential for automation, many samples could be processed in a short time. Investigators could use this assay to screen many potential anti-TB drugs.

T10B9 for the treatment of acute kidney graft rejection: NIAID-supported clinical research proved that the drug, T10B9, can reverse acute kidney graft rejection as effectively as currently available treatments while provoking fewer and less severe side effects. NIAID invested \$1.7 million in T10B9 research; the use of T10B9 to treat acute kidney graft rejection could save approximately \$40 million per year in reduced hospital and other medical care costs when compared with the current standard therapy.

Evaluation of new treatments to improve kidney transplantation in children: Kidneys are the most commonly transplanted organs worldwide. Children usually undergo kidney transplants to correct congenital defects or diabetes-related complications. Children have poorer one-year graft survival than adults, however, because their immune systems respond differently to immunosuppressive therapeutic regimens developed for use in adults. NIAID-funded scientists at thirty-two medical centers are studying new treatments to prevent the rejection of transplanted kidneys in children. During the life of a normal transplanted kidney, the medical costs of a successful kidney transplant are much less than the costs of a chronic dialysis patient. In addition, the quality of life of patients receiving transplants is improved compared with that of patients undergoing dialysis.

Hepatitis A vaccine developed and licensed: NIAID intramural investigators developed, patented and licensed a strain of hepatitis A virus (HAV) for use in the first commercially available vaccine against HAV. Worldwide, there are more than 1.4 million cases of hepatitis A each year. While most cases occur in countries with poor sanitation, thirty to fifty million persons from industrialized countries annually visit a developing country where hepatitis A is endemic. In the United States, hepatitis A accounts for more than one-half of reported hepatitis cases and costs more than \$200 million annually in medical costs and lost wages. Before the availability of this vaccine, only passive immunization with blood-derived immunoglobulin could offer protection against HAV and then only for two to five years. With a booster in six to twelve months, we expect that the vaccine will protect against HAV for up to ten years. The vaccine is now registered/licensed in forty-one countries worldwide and in 1994, generated \$110 million in international sales.

Collaborations With Industry That Result in Products That Benefit the Public Health

Scientific advances from research in Government-sponsored laboratories not only can improve health care, but also can result in commercial products and creation of jobs to develop and market these products. Technology transfer between NIAID and private industry results in the transfer of useful research advances and important resources to the scientific community and the public. NIAID has developed a substantial technology portfolio that interacts with industry and academia and transfers the Institute's technology to the private sector for commercialization. These collaborations lead to marketable products that benefit the public health. The NIAID owns more than 100 active patent properties. Patents provide an incentive for private industry to develop and market a government invention and thus make it available to the public. In addition, the NIAID has 35 Cooperative Research and Development Agreements (CRADAs). CRADAs are research and development projects undertaken jointly by NIAID and industry to enhance product development; thus allow the Institute to assign technology, patent, and licensing rights to a collaborator before the collaboration begins, and provide that inventors and their federal laboratories share any royalties resulting from federally funded research.

National Institute of Allergy and Infectious Diseases

Extramural Research

 Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act.

Budget Authority:

<u>FY 1995</u> <u>Actual</u>	<u>FY 1996</u> <u>Appropriation</u>	<u>FY 1997</u> <u>Estimate</u>	<u>Increase</u> <u>or</u> <u>Decrease</u>
\$435,318,000	\$468,661,000	\$479,413,000	+\$10,752,000

The NIAID supports research that prevents a broad spectrum of infectious diseases, disorders of the immune system, and allergic diseases. As a result, NIAID research reduces the impact of these diseases on public health. To achieve this outcome, the NIAID provides research grant, contract and cooperative agreement support to scientists at universities and other research institutions to conduct basic, applied, and clinical biomedical research. The Institute has drawn on its foundation of basic research to meet the scientific challenges posed by new and re-emerging health threats, such as AIDS, tuberculosis, CFS, Lyme disease, hantavirus, and malaria.

The NIAID Extramural Research Program is committed to supporting basic research studies on infectious and immunologic diseases. This basic research translates into prevention and treatment strategies for sexually transmitted diseases, asthma, allergies, parasitic, and fungal diseases; it results in improved diagnostics for infectious diseases and better evaluations of antiviral drugs; it fosters an improved understanding of transplantation immunology.

Funding for NIAID's non-AIDS Extramural Research program during the last five years has been as follows:

	<u>Amount</u>
FY 1992	413,431,000
FY 1993	422,699,000
FY 1994	422,771,000
FY 1995	435,318,000
FY 1996	468,661,000

Rationale for the Budget Request

The FY 1997 budget request of \$479,413,000 for the NIAID extramural research program represents an increase of \$10,752,000, or 2.3 percent over the FY 1996 level. Within the

FY 1997 request level, funds will support the following budget activities: Allergy, Immunology, and Transplantation for \$174,937,000 an increase of \$3,924,000 or 2.3 percent over the FY 1996 estimate of \$171,013,000 and Microbiology and Infectious Diseases for \$304,476,000 an increase of \$6,828,000 or 2.3 percent over the FY 1996 estimate of \$297,648,000. The following provides a brief overview of the research activities in these areas and describes some major research activities we will pursue in FY 1997:

Basic Research. The NIAID will foster basic research to reveal new methods of immune intervention and to unmask new approaches for treating and preventing human autoimmune, allergic, and inflammatory diseases. Basic research by NIAID-supported scientists in molecular structure and function, host/pathogen interaction, genetics, and physiological and biochemical processes of bacteria, viruses, fungi and parasites will lead to increased understanding of the body's protective needs. In addition, we will continue funding studies on microbial pathogens to extend basic insights needed to identify specific protective factors and to examine mechanisms of emergence, infection, pathogenicity, and virulence.

Emerging Infectious Diseases. Infectious diseases have continued to emerge in recent years, impinging on the public health and escalating health care costs. There are several reasons why new infectious diseases are emerging. Two important factors are biochemical changes in the microbial agent or vector population and changes in the human population or behavior. By supporting a broad portfolio of infectious diseases research, the NIAID is poised to achieve its research goals of understanding the epidemiology, pathogenesis, and microbiology of emerging infectious diseases. This understanding will lead to developing treatment and prevention regimens.

Ongoing and future NIAID activities relevant to emerging infectious diseases include support of basic and applied research on: new and improved diagnostics for infectious agents and development of antivirals; more effective therapeutic interventions, particularly for those strains that have developed antibiotic resistance, to include prevention and treatment, and the study of tropical diseases such as malaria and arthropod-borne viral diseases that pose a threat to developed countries.

Transplantation. Using new technology, NIAID-supported investigators have identified the sequence of human antigens that stimulate immune responses in two clinically relevant situations. The first is a tumor-related antigen that is present on melanoma cells. The second is a minor histocompatibility antigen that differs in sequence between individuals, and therefore can stimulate an immune response when expressed on transplanted tissues. These results represent significant advances for immune modulation as they demonstrate the feasibility of identifying the specific antigen sequences that initiate immune responses. We can apply this very powerful general approach, therefore, to tumor immunology, autoimmunity, transplantation and vaccine development to design antigen-specific intervention protocols.

In 1997, NIAID will be looking to improve graft survival rates in both children and adults. We will support research using the SCID-hu mouse model system, in which human cells can develop without being rejected and we can control organ transplantation without risk to patients,

to test the efficacy of new therapeutic agents for curing infections and preventing graft rejection. Investigators will examine new treatments to prevent the rejection of transplanted kidneys in children at more than thirty medical centers as part of the first such cooperative trial supported by NIAID. This will enable scientists to develop less toxic and more effective drugs to fight graft rejections, benefiting the hundreds of children who undergo kidney transplants each year in the United States and the thousands throughout the world.

NIAID will renew its cooperative clinical trials to evaluate the most promising tolerance inducing regimens for adult kidney transplant recipients. Once achieved, kidney transplant recipients will no longer have to use toxic and expensive immunosuppressive drugs for the rest of their lives.

Sexually Transmitted Diseases (STDs). Topical microbicides are safe, effective chemicals that a woman can use in her vagina before sexual intercourse to thwart microbes that cause diseases such as gonorrhea, syphilis, genital herpes, chlamydia, trichomona, hepatitis B, and HIV infections. An estimated twelve million Americans acquire a sexually transmitted disease each year, a disproportionate number of whom are women, including 40,000 new cases of infection with HIV. Adolescents and young adults under the age of twenty-five account for 63 percent of these cases, and HIV is now the fourth leading cause of death among women aged twenty-five to forty-four in the United States. Infections in newborns include syphilis, herpes, an eye disease that can lead to blindness called gonococcal conjunctivitis, and chlamydial pneumonia, an infection of the lungs that can develop into a chronic respiratory disease. The successful development of these products will empower women to take control of their own reproductive health and significantly reduce the incidence of STDs and HIV.

We have established three new research projects to develop new topical microbicides that will block the transmission of HIV and other STD agents. A major goal of these projects is to develop safe antimicrobial products that effectively fight a combination of infectious agents, whether they are viral, bacterial or protozoan. In addition, we established seven national Sexually Transmitted Diseases Cooperative Research Centers (STD CRCs) to support collaborative multidisciplinary studies on these serious infections.

Chronic Fatigue Syndrome (CFS). The physiologic basis for the profound and disabling fatigue experienced by individuals with CFS remains unexplained. Scientists active in this field of research now believe that CFS is due to multiple rather than a single etiological cause. As CFS investigators analyze the clinical, immunological, microbiological, physiological, neurological and neuropsychological characteristics of CFS patient populations from different regions, they are considering a more process oriented hypothesis for CFS etiology, possibly a neuroendocrine disturbance with multiple etiologies that could be either infectious or noninfectious.

The NIAID continues to support two CFS Cooperative Research Centers (CRCs) and many individual CFS research projects. The CFS CRCs will continue to study physiological function and comparisons of sudden versus gradual onset of illness. New proposals include studies assessing exercise challenge to explore both pathogenesis and recovery; comparing severe and moderate CFS illness; using twins to look at neuroendocrine, immunological, virological,

biological and psychosocial functions and investigating the impact of exercise on cytokine levels and virus activity. In collaboration with the Department of Veterans Affairs, we will compare CFS patients with Gulf War Syndrome patients since there is some overlap of symptoms between these illnesses.

Lyme Disease. Lyme disease continues to be a topic of very high priority as it is the most contagious common tick-borne infection in the United States. The etiologic agent, *Borrelia burgdorferi*, is very difficult to detect in infected individuals and signs and symptoms may be easily confused with other tick-borne diseases. NIAID will continue to emphasize basic research studies such as immunity, diagnostic and therapeutic strategies, epizootiology/ecology, vaccine candidates and animal models. We will encourage field research and studies in vector biology, such as applying remote sensing technologies to the study of tick vector distributions in Lyme endemic areas. In 1997, NIAID will address critical issues in recognizing and treating chronic manifestations of Lyme disease and assessing the current OspA-based vaccine trials, and we will study the bacterium that causes Lyme disease and how it interacts with the immune system to thwart the body's defenses and cause disease. In addition, we will continue our contracts to study the pathogenesis of experimental Lyme arthritis in a canine model and chronic Lyme disease in a murine model. We will continue our treatment trials for chronic Lyme disease patients and cooperate with other NIH institutes, federal agencies and organizations in the private and public sectors concerned about Lyme disease.

Parasitic Diseases. Leishmaniasis is a protozoal infection that can produce a range of disease from self-limiting cutaneous ulcers to extensive visceral disease that is invariably fatal if not treated. NIAID-supported investigators have shown that the administration of the cytokine IL-12 with the drug petostam not only resulted in elimination of the parasite infection from infected mice but was associated with the development of long-term resistance. Interleukin 12 may have a future utility as a component of combination therapy to eliminate infection and to enhance protective immune responses. This demonstration of the ability to alter the nature of an immune response has important implications not only for non-healing forms of leishmaniasis but also for other chronic, immunologically-mediated diseases.

Doctors detected an unusual form of leishmaniasis in soldiers stationed in the Persian Gulf and returning from Operation Desert Shield/Desert Storm. We call this disease viscerotropic leishmaniasis (VTL), and it differs from classical visceral leishmaniasis (VL). VTL is caused by *L. tropica*, a parasite that normally presents clinically with cutaneous manifestations. To date, confirmation of VTL has required invasive procedures to isolate parasites from spleen, liver, bone marrow or lymph nodes. VTL patients exhibit low serum anti-leishmanial antibody titers and therefore an elevated antibody response is not diagnostically useful. Thus, a simplified, sensitive serological diagnostic would be invaluable. Toward this end, NIAID-supported investigators have employed recombinant DNA technology to isolate an *L. tropica* antigen. We have characterized cellular and humoral immune responses to this antigen in patients with VTL and other forms of leishmaniasis. Further studies of this antigen should lead to its deployment in a diagnostic test for VTL infection and should expedite treatment of infected individuals.

Asthma and Allergic Diseases. NIAID plans to pursue vigorously the cause, pathogenesis, diagnosis, treatment, and prevention of allergic mechanisms in asthma and immunologic diseases by continuing to support the Asthma, Allergic and Immunologic Diseases Cooperative Research Centers and the National Cooperative Inner-City Asthma Study (NCICAS). These cooperative research programs will provide for greater coordination of targeted fundamental and clinical research on a broad range of diseases afflicting millions of Americans; they will provide for the enhancement of outreach, demonstration and education programs. These programs promote health and prevent disease through the design and assessment of medical, behavioral and educational intervention strategies for physicians and other health care providers, patients and their families, focusing in particular, on under served populations. We will target many projects to the study of asthma in the inner-city.

Despite improved treatments, asthma-related illness and deaths have increased in the United States, particularly in minority populations. NIAID funded the NCICAS to identify risk factors for asthma in inner-city children and to develop ways to reduce these risks. The program has shown that the high rate of morbidity associated with childhood asthma in this population is a multifaceted problem, including lack of access to health care, poor adherence to required treatment regimens, and psycho-social stresses. The study also showed the important role that cockroaches play as an allergen in inner-city homes. In a second phase of the study, NIAID-funded investigators are testing the effectiveness of interventions such as assignment of an asthma case manager to coordinate care and environmental controls to eradicate cockroach allergens. Anticipated results include reduced visits to an emergency room, reduced hospitalization, and less school absenteeism.

Vaccine Research and Development. The NIAID is the center of vaccine research and development within the Department of Health and Human Resources. In 1997, NIAID will continue as the lead agency for The Children's Vaccine Initiative, a program that provides scientific and programmatic direction aimed at creating a single vaccine against the multiple infectious diseases that strike infants and children. In addition, the Institute provides support for Vaccine and Treatment Evaluation Units (VTEUs) that conduct phase I and phase II human trials of safety, protective immunity, and protective efficacy of candidate vaccines.

NIAID programs promote the development of a broad array of new and improved vaccines for bacterial, viral, fungal, and parasitic pathogens involved in such diverse disorders as STDs, tropical diseases, and tuberculosis. Other disease vaccines under development include viral hepatitis, influenzae, rotaviruses, cholera, leprosy, pertussis, tetanus, and diphtheria. NIAID-supported investigators are developing a new measles vaccine that we can safely administer to infants and that can produce long-lasting immunity. Other studies have shown that vitamin A might augment the efficacy of existing vaccines by enhancing the function of the immune system. These results affect hundreds of millions of infants worldwide, and we must now develop new protocols to integrate vitamin A into the primary health care of infants, especially in developing countries where infants are often deficient in vitamin A.

In 1997, NIAID-supported investigators will continue their studies of a genetically engineered vaccine against a natural form of histoplasmosis, a major respiratory fungal disease

both in the U.S. and throughout the world. Researchers recently identified a component of the fungus that protected mice against lethal infection. We hope to validate this vaccine approach and extend it to prevent fungal infections in humans. Other NIAID-supported scientists will expand their research on an edible vaccine delivery system. Using recombinant DNA technology, several groups of NIAID-funded scientists are producing transgenic plants that contain foreign genes from hepatitis B viruses (HBV) or bacteria. Because of the repeated dietary challenge, we would expect that individuals developed long lasting mucosal immunity. This type of immunity is especially important for many forms of hepatitis and bacterial diarrheas transmitted by an oral route. We initially tried transgenics, as we call this process, in the tobacco leaf. Scientists genetically altered tobacco leaves to produce a recombinant surface antigen of HBV--the same subunit in the widely-used commercial vaccines. When isolated and injected into mice, we induced the same degree and type of immunity. Subsequently, researchers produced transgenic potatoes and they fed the raw potato to mice. Even by oral administration, the potatoes conferred immunity. A similar study using transgenic plants to confer oral immunization against an *E. coli* enterotoxin was equally successful in a mouse model. Investigators are now planning to prepare HBV and other vaccines in other edible plants, such as bananas, which do not need cooking, are easy to distribute, and palatable to infants. If successful, this novel approach would address many outstanding needs. Chief among these, we could vaccinate large populations at minimal cost, without the limitations of traditional vaccine delivery programs.

In 1997, NIAID scientists will continue their studies on pertussis. The NIAID supported a major effort to evaluate acellular pertussis vaccines through two large-scale clinical trials in Sweden and Italy. The results revealed that three new products provided excellent protection, and the products were highly effective in protecting infants against pertussis and had fewer side effects than current vaccines. This result is the culmination of more than fifteen years of NIAID efforts in the development of acellular pertussis vaccines.

National Institute of Allergy and Infectious Diseases

Intramural Research

 Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act.

Budget Authority:

FY 1995 Actual		FY 1996 Appropriation		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
582	\$76,911,000	587	\$82,128,000	587	\$82,128,000	--	\$0

The National Institute of Allergy and Infectious Diseases (NIAID) conducts in-house research through the Division of Intramural Research (DIR). DIR scientists study immunologic, allergic, and infectious diseases in NIAID laboratories in Bethesda, Rockville, and Frederick, Maryland and the Rocky Mountain Laboratories in Hamilton, Montana. The Bethesda facility also provides space for DIR's clinical activities at the NIH Clinical Center. Patients are admitted to this clinical unit to participate in new and promising treatment or diagnostic procedures derived from the basic research conducted in laboratories. Besides conducting research, DIR offers many laboratory and clinical research training opportunities for physicians and scientists who go on to positions of scientific leadership in universities across the country.

Comparable funding for the NIAID non-AIDS Intramural Research activity during the last five years has been as follows:

	<u>Amount</u>	<u>FTE</u>
FY 1992	72,206,000	653
FY 1993	75,861,000	664
FY 1994	75,750,000	636
FY 1995	76,911,000	582
FY 1996	82,128,000	587

Rationale for the Budget Request

The FY 1997 budget request of \$82,128,000 for the NIAID intramural research program represents the same level as the FY 1996 estimate. The following provides a brief overview and description of some major research activities we will pursue in FY 1997.

Lyme Disease. NIAID intramural investigators have shown that the Lyme disease bacterium, *Borrelia burgdorferi*, produces several outer surface proteins when its tick host feeds on a mammal. An increase in environmental temperature represents an important signal for this

increase in protein production. This finding is significant as one of the proteins abundantly produced, OspC, may be the first protein the immune system encounters when spirochetes enter the body. Scientists will examine how the Lyme bacterium varies its surface proteins and the role these changes play in infection.

Chronic Fatigue Syndrome (CFS). Intramural neuroendocrine studies are addressing the hypothesis that CFS may be related to a defect in the hypothalamic-pituitary-adrenal axis. A clinical trial with hydrocortisone therapy is underway. Results from this trial may provide important insights on the mechanism of CFS pathogenesis.

Autoimmune Diseases. NIAID scientists have identified a genetic mutation responsible for a novel form of autoimmune disease in children. The researchers studied a group of children with autoimmune/lymphoproliferative syndrome (ALPS), consisting of massive, nonmalignant swelling of the lymph nodes, many immune cells, called T lymphocytes, and antibody-mediated autoimmune disorders. They found that several ALPS children had mutations that caused them to produce mutant versions of the Fas protein, which normally delivers a "death signal" to T lymphocytes. Because of the mutations, these children were unable to get rid of unneeded T cells, which then proliferated and caused the disease symptoms. Results from this research may have a bearing on understanding the mechanisms of Hodgkin's disease, or Hodgkin's lymphoma, a common tumor of the lymph glands.

Chronic Granulomatous Disease (CGD). In 1997, NIAID will continue to assess the effectiveness of interferon-gamma as a treatment for patients with CGD. In ongoing clinical investigations, NIAID intramural investigators reported that they have sustained a reduction in infections and they have seen no unexpected toxicities in treated CGD patients with interferon-gamma. The drug has reduced the incidence of fungal infections in CGD patients to half that seen in CGD patients who did not receive interferon-gamma. These encouraging findings in CGD patients have prompted consideration of the use of interferon-gamma in other infectious diseases. Consequently, in 1997 NIAID will investigate whether interferon-gamma has a role in multiple drug resistant tuberculosis in patients either with or without HIV infection.

NIAID intramural scientists have also cloned all four abnormal genes that cause CGD, a genetic disorder characterized by recurrent and frequently life-threatening infections. The researchers have successfully treated all four distinct forms of CGD in the laboratory by transferring the genes for missing proteins into blood precursor cells taken from CGD patients. The laboratory studies and recent advances in the collection of immune cells from CGD patients now make a clinical trial of gene therapy feasible. Scientists may use this model system for therapy of other genetic disorders affecting bone marrow cells.

Shingles. NIAID scientists have identified the genes expressed by varicella-zoster virus (VZV) during latency in the Shingles virus. When individuals are first infected with VZV, usually in childhood, the virus causes chickenpox but then becomes dormant in the body. At some point, usually after age fifty, the virus can reactivate and cause shingles, or herpes zoster. In 1997, research targeted to identifying additional VZV genes may help scientists develop treatments that will prevent VZV from reactivating and causing shingles.

Vaccine Research and Development. In 1997, NIAID investigators will continue studies to identify the immunological mechanisms by which a candidate malarial vaccine protects against the merozoite, the form the malarial parasite is in when it invades red blood cells in an infected individual. NIAID has developed a vaccine designed to prevent the spread of malaria. We recently conducted the first human trial of this malaria transmission-blocking vaccine, which consists of a molecule found on the surface of malaria parasites, at the NIH Clinical Center. NIAID scientists have cloned genes for four of seven possible molecular candidates; two of them, Pfs25 and Pfs28, can induce transmission-blocking antibodies in laboratory animals. Preliminary evidence indicates that a vaccine consisting of both Pfs25 and Pfs28 may be more effective than either alone, so scientists are developing a vaccine consisting of sequences from both molecules.

Also, scientists will also continue research on a rotavirus vaccine that protects against severe diarrhea, which can lead to dehydration and death. In clinical trials, we prevented more than 80 percent of the most severe diarrheal illnesses caused by rotaviruses among infants by using a vaccine developed and patented by NIAID scientists. Rotaviruses are the single most important recognized cause of severe diarrhea among infants and children younger than two years of age.

Hepatitis E virus (HEV) is the most important cause of acute hepatitis among adults in some countries of Asia, Africa, and the Middle East and has caused epidemics in Mexico. Although 1 percent of those infected will die of acute liver failure, the virus can kill as many as 20 percent of infected pregnant women. NIAID intramural scientists tested whether an HEV vaccine or plasma containing HEV antibodies could prevent either hepatitis resulting from HEV infection or the infection itself in cynomolgus monkeys. They found that two doses of vaccine prevented all signs of hepatitis and HEV infection in the monkeys and that monkeys given plasma containing HEV antibodies developed HEV infection, but not hepatitis. Investigators are currently pursuing the vaccine for use in humans to prevent cases of hepatitis E in developing countries and to protect travelers to those regions.

National Institute of Allergy and Infectious Diseases

Research Management and Support

 Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act.

Budget Authority:

FY 1995 Actual		FY 1996 Appropriation		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
460	\$24,711,000	461	\$22,821,000	461	\$22,821,000	—	\$0

The Research Management and Support (RMS) activity provides the resources that contribute to the general management and policy direction of the Institute's research programs. The managerial, scientific, and administrative functions encompassed by this activity include grants and contracts management, the scientific review of grant and contract applications, scientific program management, financial management, program planning and development, personnel, information dissemination, data management, procurement, property, and technology transfer.

Funding for the Research Management and Support activity during the last five years has been as follows:

	<u>Amount</u>	<u>FTE</u>
FY 1992	25,505,000	438
FY 1993	25,969,000	472
FY 1994	24,336,000	466
FY 1995	24,344,000	460
FY 1996	22,821,000	461

Rationale for the Budget Request

The FY 1997 NIAID budget request for the Research Management and Support budget activity is \$22,821,000 the same as the 1996 estimate.

In FY 1997, NIAID management will continue to reassess the state of science in those areas within the Institute's purview. These efforts will include the review of progress and the identification of areas of unusual scientific opportunity that may lead to new approaches to support and help research. Vital to these efforts is the continued participation in and sponsorship of selected meetings, conferences, workshops, and symposia on high-priority research topics and issues, including areas of technology transfer and consensus development. These activities

provide the necessary forum to exchange and foster new information and to translate research findings to clinical care.

NIAID will draw upon the advice and counsel of its task forces, national advisory groups, blue ribbon panels and other outside experts to develop and refine the Institute's scientific agenda. This methodology was extremely beneficial in the development of the NIAID Tuberculosis Agenda and the Vaccine Development Initiatives Plan.

We will continue to emphasize outreach activities directed to health professionals, voluntary associations, and various private sector groups that extend to lay audiences or at-risk groups. The Institute will continue to work closely with minority professional associations, medical facilities and academic institutions to distribute information on the diseases and disorders that disproportionately affect minority populations; we will encourage young minority scientists to participate in the Institute's scientific mission and we will reach out to the minority scientists of tomorrow through our several student programs.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases
Budget by Mechanism

	1995		1996		1997	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects						
Noncompeting.....	1,224	274,604,000	1,165	268,548,000	1,249	291,531,000
Admin. supplemental.....	(40)	1,761,000	(40)	1,831,000	(40)	1,868,000
Competing						
Renewal.....	159	40,990,000	193	52,879,000	166	46,290,000
New.....	173	35,045,000	251	52,981,000	211	45,201,000
Supplemental.....	—	—	—	—	—	—
Subtotal.....	332	76,035,000	444	105,860,000	377	91,491,000
Subtotal.....	1,556	352,400,000	1,609	376,239,000	1,626	384,890,000
SBIR/STTR.....	51	9,102,000	58	10,097,000	68	12,211,000
Subtotal, research projects.....	1,607	361,502,000	1,665	386,336,000	1,694	397,101,000
Research centers						
Specialized/comprehensive.....	3	1,466,000	3	1,600,000	3	1,600,000
Research Centers in						
minority institutions.....	—	—	—	—	—	—
Subtotal, research centers.....	3	1,466,000	3	1,600,000	3	1,600,000
Other research						
Research career program.....	114	8,887,000	117	9,490,000	115	9,490,000
Minority biomedical research						
support.....	—	593,000	—	633,000	—	633,000
Other.....	19	870,000	20	721,000	20	721,000
Subtotal, other research.....	133	10,150,000	137	10,844,000	135	10,844,000
Total, research grants.....	1,743	373,118,000	1,805	398,780,000	1,832	409,545,000

Training						
Individual awards						
Noncompeting.....	56	1,545,000	41	1,171,000	80	2,335,000
Competing, new.....	38	1,014,000	56	1,561,000	17	457,000
Subtotal, individual.....	94	2,559,000	97	2,732,000	97	2,792,000
Institutional awards						
Noncompeting.....	450	11,536,000	501	13,281,000	501	13,591,000
Competing						
Renewal.....	50	1,757,000	37	1,293,000	37	1,310,000
New.....	51	1,198,000	35	898,000	35	911,000
Subtotal, institutional.....	551	14,491,000	573	15,472,000	573	15,812,000
Total Training.....	645	17,050,000	670	18,204,000	670	18,604,000
R&D Contracts (SBIR/STTR)						
.....	63	45,150,000	70	51,677,000	68	51,264,000
Intramural research						
Research management and support.....	582	76,911,000	587	82,128,000	FTEs 587	82,128,000
.....	460	24,711,000	461	22,821,000	461	22,821,000
.....	1,042	536,940,000	1,048	573,610,000	1,048	584,362,000
Clinical Trials.....						
.....		(45,381,000)		(47,196,000)		(48,140,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		FY 1997		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTE	Amount
Extramural Research:												
Allergy, immunology and transplantation...	—	\$154,725	—	\$153,436	—	\$158,847	—	\$171,013	—	\$174,937	—	+\$3,924
Microbiology and infectious diseases...	—	287,861	—	289,327	—	276,471	—	297,648	—	304,476	—	+6,828
Subtotal.....	—	422,586	—	422,763	—	435,318	—	468,661	—	479,413	—	+10,752
Intramural research.....	664	75,861	636	75,750	582	76,911	587	82,128	587	82,128	—	—
Research management and support.....	472	25,969	468	24,336	460	24,711	461	22,821	461	22,821	—	—
Total Obligations.....	1,136	524,416	1,102	522,849	1,042	536,940	1,048	573,610	1,048	584,362	—	+10,752
Unobligated balance lapsing.....		113		8								
Total, budget authority, 1,136	524,529		1,102	522,857	1,042	536,940	1,048	573,610	1,048	584,362	—	+10,752

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Summary of Changes

1996 Estimated budget authority.....	\$573,610,000
1997 Estimated budget authority.....	<u>584,362,000</u>
Net change.....	+10,752,000

	1996 Current Estimate Base Budget (FTEs)	Change from Base Budget (FTEs) Authority
Changes:		
A. Built-in:		
1. Intramural		
a. Within grade increase.....	\$34,303,000	+\$501,000
b. Annualization of FY 1996 pay raise.....	34,303,000	+218,000
c. January 1997 pay raise.....	34,303,000	+772,000
d. Unemployment and FECF increase.....	34,303,000	+4,000
e. Payment for centrally furnished services.....	13,071,000	-28,000
f. Service and supply fund increase.....	4,136,000	+91,000
g. Increased cost of laboratory materials and supplies.....	30,618,000	+719,000
		<u>+2,277,000</u>
2. Research Management and Support		
a. Within grade increase.....	14,706,000	+215,000
b. Annualization of FY 1996 pay raise.....	14,706,000	+93,000
c. January 1997 pay raise.....	14,706,000	+331,000
d. Unemployment and FECF increase.....	14,706,000	+3,000
e. Payment for centrally furnished services.....	3,017,000	-48,000
f. Service and supply fund increase.....	773,000	+17,000
g. Increased cost of laboratory materials and supplies.....	4,325,000	+106,000
		<u>+717,000</u>

Summary of Changes continued

B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a) Noncompeting.....	1,165	\$270,379,000	+84	+\$23,020,000
b) Competing.....	444	105,860,000	-67	-14,369,000
c) SBIR/STTR.....	56	10,097,000	+12	+2,114,000
Subtotal.....	1,665	386,336,000	+29	+10,765,000
2. Special/Comp Centers.....	3	1,600,000	---	---
3. Other research.....	137	10,844,000	-2	---
4. Research Training.....	670	18,204,000	---	+400,000
5. R & D Contracts	70	51,677,000	-2	-413,000
Subtotal, extramural.....	2,545	468,661,000	+25	+10,752,000
	(FTEs)	Amount	(FTEs)	Amount
7. Intramural research.....	587	82,128,000	---	-2,277,000
8. Research Management and Support.....	461	22,821,000	---	-717,000
Total, changes.....			---	+10,752,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Object

	FY 1996 <u>Estimate</u>	FY 1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Full-time equivalent employment.....	1,048	1,048	—
Full-Time equivalent of overtime and holiday hours.....	1	1	—
Average ES salary.....	\$108,774	\$112,037	+\$3,263
Average GM/GS grade.....	10.0	10.0	—
Average GM/GS salary.....	47,012	48,422	+1,410
Average salary, grades established by act of July 1, 1994 (42 U.S.C. 207).....	77,578	79,905	+2,327
Average salary of ungraded positions.....	28,900	29,767	+867
Personnel compensation:			
Permanent positions.....	\$26,313,000	\$27,460,000	+\$1,147,000
Positions other than permanent.....	6,611,000	6,899,000	+288,000
Other personnel compensation.....	1,599,000	1,669,000	+70,000
Special personnel services.....	<u>5,514,000</u>	<u>5,754,000</u>	<u>+240,000</u>
Subtotal, personnel compensation.....	40,037,000	41,782,000	+1,745,000
Personnel benefits.....	8,836,000	9,222,000	+386,000
Benefits for former personnel.....	136,000	142,000	+6,000
Travel and transportation of persons.....	955,000	886,000	-69,000
Transportation of things.....	210,000	195,000	-15,000
Rental Payments to GSA.....	1,505,000	1,550,000	+45,000
Rental Payments to others.....	416,000	428,000	+12,000
Communications, utilities and miscellaneous charges.....	1,309,000	1,348,000	+39,000

Budget Authority by Object -- continued

Printing and reproduction.....	\$181,000	\$168,000	-\$13,000
Consultant services.....	125,000	116,000	-9,000
Other Services.....	14,234,000	13,211,000	-1,023,000
Purchases from government accounts.....	24,990,000	24,779,000	-211,000
R & D Contracts.....	51,281,000	50,868,000	-413,000
Medical care.....	432,000	401,000	-31,000
Operation and maintenance of equipment....	1,187,000	1,101,000	-86,000
Supplies and materials.....	8,203,000	7,612,000	-591,000
Equipment.....	2,430,000	2,255,000	-175,000
Lands & Structures.....	13,000	13,000	—
Grants, subsidies & contributions.....	416,984,000	428,149,000	+11,165,000
Insurance Claims.....	142,000	132,000	-10,000
Interest and Dividends.....	<u>4,000</u>	<u>4,000</u>	<u>—</u>
Total.....	573,610,000	584,362,000	+10,752,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Administrative Costs

	1996 Estimate	1997 Estimate	Change
Personnel compensation:			
Permanent positions (11.1).....	\$26,313,000	\$27,460,000	+\$1,147,000
Positions other than permanent (11.3).....	6,611,000	6,899,000	+288,000
Other personnel compensation (11.5).....	1,599,000	1,689,000	+70,000
Special personnel services (11.8).....	<u>5,514,000</u>	<u>5,754,000</u>	<u>+240,000</u>
Total, personnel compensation (11.9).....	40,037,000	41,782,000	+1,745,000
Personnel benefits (12.1).....	8,836,000	9,222,000	+386,000
Benefits for former personnel (13.0).....	136,000	142,000	+6,000
Travel (21.0).....	995,000	886,000	-109,000
Transportation of things (22.0).....	210,000	195,000	-15,000
Rental payments to others (23.2).....	416,000	428,000	+12,000
Communications, utilities and miscellaneous charges (23.3).....	1,309,000	1,348,000	+39,000
Printing and reproduction (24.0).....	181,000	168,000	-13,000
Consultant services (25.1).....	125,000	116,000	-9,000
Other services (25.2).....	14,234,000	13,211,000	-1,023,000
Purchases from government accounts (25.3).....	20,854,000	20,456,000	-398,000
Medical care (25.6).....	432,000	401,000	-31,000
Operation and maintenance of equipment (25.7)....	1,187,000	1,101,000	-86,000
Supplies and materials (26.0).....	<u>8,203,000</u>	<u>7,612,000</u>	<u>-591,000</u>
Total.....	97,155,000	97,068,000	-87,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports1996 House Appropriations Committee Report LanguageItem

Asthma - The House in its report 104-209, page 67 stated, -- "The Committee is pleased with the continued activities of the National Cooperative Inner City Asthma Study, a comprehensive effort in eight cities to design and evaluate intervention programs to counter risk factors for inner city asthmatic children. The Committee urges continued attention to pediatric asthma, especially as it affects minority children."

Action Taken or To Be Taken

The National Cooperative Inner City Asthma Study comprises eight centers studying asthma in minority children living in the inner city. In Fiscal Year 1996 the NIAID renewed this program for five years. The continuation of this study will include new educational programs aimed at physicians and will focus greater attention on the relationship between the environment and asthma morbidity in minority children.

Item

Hemophilia - The House in its report 104-209, page 68 stated, -- "The Committee fully supports NIAID's continuing commitment to provide access to HIV/AIDS clinical trials for hemophilia patients, utilizing the existing network of hemophilia treatment centers, through the "ACTU without walls" clinical trials program."

Action Taken or To Be Taken

The NIAID will continue to provide access to HIV/AIDS clinical trials for hemophilia patients using existing networks of hemophilia treatment centers through the ACTU without walls clinical trials program.

Item

Microbicides - The House in its report 104-209, page 68 stated, -- "The Committee acknowledges the progress that NIAID has made in funding research on microbicides for STD/HIV prevention. Of note are the establishment of program projects for topical microbicide research and clinical studies to evaluate existing and new products. The Committee believes that

safe, effective topical microbicides are urgently needed to prevent the spread of STDs and HIV infection for both women and men. The Committee continues to encourage NIAID to make funding for the major areas of microbicide research a priority, including funding for basic research, product development, clinical evaluation, and behavioral research."

Action Taken or To Be Taken

In Fiscal Year 1996 the NIAID launched program projects on topical microbicides to further address the urgent need for safe, effective topical microbicides for the prevention of STDs and HIV. Through this initiative and other research efforts, the NIAID will continue to provide support for topical microbicides research, including funding for basic research, product development, clinical evaluation, and behavioral research.

Item

Women's Interagency HIV Study (WIHS) - The House in its report 104-209, page 68 stated, -- "The Committee applauds the speed with which the WIHS has begun to enroll women and to obtain the needed data. The Committee urges continued funding for this study so that women can be followed prospectively to obtain the information critical to treatment and prevention efforts. The Committee believes that it is important to achieve geographical representation and to include an adequate number of women in the study to answer these important questions."

Action Taken or To Be Taken

The NIAID continues to support the Women's Interagency HIV Study (WIHS) ensuring that we enroll an appropriate number of women in the study and that we achieve appropriate geographical representation.

Item

Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) - The House in its report 104-209, page 68 stated, -- "The Committee encourages NIAID to consider appointing a CFIDS coordinator with institute-wide authority to provide leadership on CFIDS. The Committee looks forward to the deliberations of the NIAID Advisory Council meeting scheduled for the fall of 1995 which will focus on promising CFIDS research."

Action Taken or To Be Taken

In 1991, at the request of Congress, Dr. John R. La Montagne, Director, Division of Microbiology and Infectious Diseases, NIAID was appointed by the Acting Director, NIH as the NIH Coordinator for Chronic Fatigue Syndrome. The NIH CFS Coordinator, through the NIH CFS Coordinating Committee facilitates communications among NIH institutes regarding extramural and intramural CFS activities; provides reporting regarding NIH CFS research activities to the Department of Health and Human Services, the Congress and various

constituency groups; enhances the sharing of multidisciplinary expertise in the formulation of recommendations regarding NIH CFS activities; assists in the development of complementary research programs and provides NIH-wide awareness of CFS research needs and policy issues.

In the fall of 1995 the National Advisory Allergic and Infectious Diseases Council convened to review the NIAID CFS research program. The Council commended the NIAID for its leadership in establishing a multidisciplinary approach to studying CFS and encouraged the NIAID to retain overall NIH leadership in this area.

1996 Senate Report Language

Item

Lyme Disease - The Senate in its report 104-145, page 82, stated, -- "The Committee acknowledges the NIAID's efforts in the area of diagnostic test development, prevention strategies, and the early treatment of disease. The Committee is particularly heartened by NIAID's efforts of the last year to lay the groundwork for intensive study of the phenomenon of chronic Lyme disease and strongly encourages the NIAID to expand its efforts in this direction. The Committee requests that NIAID be prepared to report on its progress during the 1997 budget hearings."

Action Taken or To Be Taken

In Fiscal Year 1996 the NIAID launched a new initiative studying treatment trials for chronic Lyme disease patients. In Fiscal Year 1997 the NIAID will expand on this program by bringing chronic Lyme disease patients to the NIH Clinical Center for evaluation and treatment. The NIAID will also work with the CDC and FDA to address issues in recognizing and treating chronic manifestations of Lyme disease.

Item

Chronic Fatigue and Immune Dysfunction Syndrome -The Senate in its report 104-145, page 83, stated, -- "The Committee believes that NIH can maximize its research efforts by investing in a CFIDS (CFS) Coordinator with institute-wide authority to provide leadership on CFIDS (CFS) and by continuing to secure attention to CFIDS (CFS) research through the small grants program. The Committee looks forward to the results of the NIAID Advisory Council meeting scheduled for the fall of 1995 that focuses on CFIDS."

Action Taken or To Be Taken

Same response as in "1995 House Appropriations Committee Report Language", Chronic Fatigue Immune Dysfunction Syndrome.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1996 Amt. Authorized	1996 Estimate	1997 Amt. Authorized	1997 Budget Request
Research and Investigation	Section 301	42s241	Indefinite--		Indefinite--	
National Institute of Allergy and Infectious Diseases	Section 446	42s285f	Indefinite--	\$555,406,000		\$565,758,000
National Research Service Awards	Section 487	42s288-1	Such Sums as Necessary	18,204,000	Authorization Pending	18,604,000
Total Budget Authority				\$573,610,000		\$584,362,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u>	<u>1/</u>
1988	\$551,102,000	\$439,667,000	\$661,458,000	\$638,800,000	
1989	435,084,000	732,453,000	758,352,000	744,152,000	
1990	442,596,000	845,523,000	847,112,000	843,745,000	
1990 Sequester				-10,768,000	
1991	886,875,000	944,965,000	904,010,000	906,251,000	
1991 Sequester				-12,000	
1992	976,711,000	972,830,000	965,952,000	959,914,000	
1993	1,010,845,000	990,055,000	989,055,000	979,471,000	
1994	1,065,583,000	1,065,583,000	1,065,583,000	1,063,704,000	
1995	542,864,000	535,847,000	535,847,000	535,847,000	
1995 Rescission				-648,000	
1996	557,354,000	1,169,628,000	549,246,000	1,169,628,000	
1997	584,362,000				

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ The 1989 request excludes funds for AIDS research (\$310,268,000) proposed for Consolidation in the Office of the Assistant Secretary for Health.

- 4/ Excludes \$13,537,000 in NRSA training programs not considered.
- 5/ The 1990 request excludes funds for the National HIV program (\$400,116,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
- 6/ Excludes enacted administrative reduction of \$2,573,000.
- 7/ Excludes enacted administrative reductions of \$26,986,000.
- 8/ Excludes enacted administrative reductions of \$11,197,000.
- 9/ Excludes enacted administrative reductions of \$12,334,000.
- 10/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research.
- 11/ Excludes enacted administrative reductions of \$308,000, \$4,000, and \$257,000.
- 12/ A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on levels provided in three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

National Institute of Allergy and Infectious Diseases
Detail of Full-Time Equivalent Employment (FTE)

	FY 1995 <u>Actual</u>	FY 1996 <u>Estimate</u>	FY 1997 <u>Estimate</u>
Office of the Director.....	177	177	177
Division of Intramural Research.....	582	587	587
Division of Extramural Activities.....	96	96	96
Division of Allergy, Immunology, and Transplantation.....	19	19	19
Division of Acquired Immunodeficiency Syndrome.....	115	116	116
Division of Microbiology and Infectious Diseases.....	<u>53</u>	<u>53</u>	<u>53</u>
TOTAL NIAID.....	1,042	1,048	1,048

Average GS/GM Grade

1992.....	10.1
1993.....	10.0
1994.....	10.0
1995.....	10.0
1996.....	10.0
1997.....	10.0

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute of Allergy and Infectious Diseases
Detail of End-of-Year Employment

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Executive Level I.....	--	--	--
Executive Level II.....	--	--	--
Executive Level III.....	--	--	--
Executive Level IV.....	--	--	--
Executive Level V.....	--	--	--
Subtotal.....	--	--	--
Total - Exec. Level Salary.....	--	--	--
ES-6.....	--	--	--
ES-5.....	5	5	5
ES-4.....	6	6	6
ES-3.....	3	3	3
ES-2.....	--	--	--
ES-1.....	1	1	1
Subtotal.....	15	15	15
Total - ES Salary.....	\$1,591,200	\$1,631,616	\$1,680,565
GS/GM-15.....	68	68	68
GS/GM-14.....	98	98	98
GS/GM-13.....	88	88	88
GS-12.....	115	115	115
GS-11.....	118	118	118
GS-10.....	--	--	--
GS-9.....	75	75	75
GS-8.....	24	24	24
GS-7.....	85	87	87
GS-6.....	42	44	44
GS-5.....	19	21	21
GS-4.....	28	31	31
GS-3.....	3	3	3
GS-2.....	7	7	7
GS-1.....	4	4	4
Subtotal.....	774	783	783

	1995 Actual	1995 Estimate	1996 Request
Grades established by Act of July 1, 1994 (42 U.S.C. 207)			
Assistant Surgeon General.....	1	1	1
Director Grade.....	--	--	--
Senior Grade.....	29	29	29
Full Grade.....	12	12	12
Senior Assistant Grade.....	29	29	29
Assistant Grade.....	7	7	7
Subtotal.....	78	78	78
Ungraded.....	41	41	41
Total Permanent Positions.....	908	917	917
Total Positions, End of Year.....	1,077	1,086	1,086
Total Full-Time Equivalent (FTE) Employment, End of Year	1,042	1,048	1,048
Average ES level.....	3.9	3.9	3.9
Average ES salary.....	\$106,080	\$108,774	\$112,037
Average GS/GM grade.....	10.0	10.0	10.0
Average GS/GM salary.....	\$45,847	\$47,012	\$48,422

TUESDAY, APRIL 23, 1996.

**NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE
AND KIDNEY DISEASES**

WITNESSES

DR. PHILLIP E. GORDEN, DIRECTOR

**DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
L. EARL LAURENCE, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF DI-
ABETES AND DIGESTIVE AND KIDNEY DISEASES**

CHARLES R. ZELLERS, FINANCIAL MANAGEMENT OFFICER

**DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET,
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Mr. PORTER. Now we will hear from the National Institute of Diabetes and Digestive and Kidney Diseases. And we're very pleased to welcome Dr. Phillip Gorden, the Director. Dr. Gorden?

INTRODUCTION OF WITNESSES

Dr. GORDEN. Thank you, Mr. Chairman.

I'd like to briefly introduce my colleagues. To the back here is Mr. Zellers, our Budget Officer. To my right, Mr. Laurence, our Deputy Director for Management. You know Dr. Varmus and Mr. Williams.

OPENING STATEMENT

Mr. Chairman, I'm very pleased to have the opportunity to testify about research progress and plans of the NIDDK and our very broad and challenging research mission. Consistent with maintaining core support for all of our programs, we have made every effort to streamline our activities in order to take maximum advantage of emerging scientific opportunity. Today I will highlight just a few major discoveries and programs that have evolved from focusing on such opportunities.

LEPTIN AND THE OBESITY GENE

A prime example is the discovery of a strikingly similar obesity gene in rodents and humans, genes that may hold the key to appetite and weight. These genetic studies have led to the discovery of the hormone leptin, thought to be a pivotal regulator of both appetite and energy utilization. Leptin is produced in fat cells, circulates in the bloodstream and binds to receptors in the brain.

This interaction then regulates a complex network that controls both the satiety and food utilization. Mutations in the gene for leptin clearly cause obesity in rodents. This information has already permitted early human studies. Most important in this example, however, is the rapidity in the progress of the discovery from the gene defect to the hormone to the biotechnology of produc-

tion of leptin, a seminal research tool and possibly an important prototype for pharmaceuticals useful in the treatment of obesity.

The progress I am describing today is the culmination of decades of basic research on a specific initiative NIDDK launched over four years ago, in anticipation of the increasing prevalence of obesity in the United States. Our longstanding commitment to pursue opportunities in the basic sciences also has enabled us to undertake major new clinical trials of exceedingly high importance to the health of the American people.

DIABETES CLINICAL TRIALS

These include, one, a primary prevention trial in insulin-dependent or juvenile diabetes, which would use new technology to immunize or tolerize against the immunologic attack on insulin producing cells. Second, a primary prevention trial in non-insulin-dependent diabetes, which will include a large minority population and will employ both lifestyle changes and newly developed drugs to decrease insulin resistance, in order to prevent or delay the onset of diabetes. And three, a new trial in benign prostatic hyperplasia, which will use newly developed drugs for non-surgical treatment to capitalize on the opportunity to learn more about this increasingly important problem in an aging population. In all of these clinical trials we've forged important collaborations with industry that have enhanced our resource base, and would not have been possible without an NIH initiative.

CYSTIC FIBROSIS

Diagnosis of cystic fibrosis was once a childhood death sentence, but today CF patients survive well into adulthood. The quality of their lives has been significantly improved.

These dramatic changes are the result of long term basic and clinical research. Most recently, the cloning of the CF gene and identification of its protein product have provided a revolutionary opportunity to understand this disease as a molecular abnormality, and form the basis for early stages in gene therapy.

POLYCYSTIC KIDNEY DISEASE

By deploying the power of new molecular tools to define genetic and metabolic disorders, we've discovered the gene for polycystic kidney disease. With the gene in hand, we have already elucidated its product, the protein polycystin. We now have the opportunity to find the protein's function and how the mutated, abnormal form causes PKD, which is responsible for up to 8 percent of end stage renal disease. These discoveries open new opportunities for therapeutic targets.

ERYTHROPOIETIN

The return also has been great from our investment in basic research in hematology. For example, our research led to the biotechnology industry's ability to genetically engineer, produce and market a drug called erythropoietin. This is a growth factor for red blood cells which has proven enormously beneficial in the treat-

ment of the anemia of end stage renal disease, AIDS, and sickle cell disease.

HELICOBACTER PYLORI

Cost saving health benefits have emerged from the discovery that duodenal ulcers are caused by a bacterium, *Helicobacter pylori*, which can be easily and inexpensively eradicated by drug therapy. It's been estimated that \$400 million to \$800 million annually can be saved by preventing ulcer recurrence alone. By studying molecular genetics and the bacteriology of *H. pylori* infection, we are gaining insights about the relationships between specific virulence factors and disease, including gastric cancer.

Clearly, basic research yields enormous benefits. This is why we continue to invest in the neurosciences, including the role of brain hormones in health and disease. This is why we will continue to support basic intramural research on structural biology, to disclose the three dimensional architecture of molecules that are important in diseases ranging from diabetes to cancer. This is why we will fund basic studies of bone metabolism that are vital to our understanding of diseases such as osteoporosis, as well as the fundamental studies of growth factors and hormones that may play a key role in breast and prostate cancers.

TRANSGENIC ANIMAL MODELS

Similarly, we will maintain a strong commitment to developing transgenic animal models to give us clues about the wide range of diseases, including inflammatory bowel disease. We are sustaining our efforts also in the basic research of women's urologic disorders, including interstitial cystitis and incontinence.

Mr. Chairman, we believe that today's portfolio of basic research is the wellspring for clinical trials, drug development and health care improvements of the future. Our fiscal 1997 budget request for the NIDDK is \$772,975,000. I would be very pleased to answer any questions.

[The prepared statement and biography of Dr. Phillip Gorden follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Diabetes and Digestive and Kidney Diseases

I am very pleased to have the opportunity to testify about the research progress and plans of the NIDDK and our very broad and challenging research mission. Our research focuses on diabetes and other endocrine diseases; metabolic diseases such as cystic fibrosis; polycystic and other diseases of the kidney; urologic diseases including the bladder and prostate; sickle cell disease, Cooley's anemia and other blood disorders; a wide range of digestive disorders such as inflammatory bowel disease; and nutritional disorders, including obesity. Consistent with maintaining core support for all our programs, we have made every effort to streamline our activities in order to take maximum advantage of emerging scientific opportunities. Today, I will highlight just a few major discoveries that have evolved from pursuing such opportunities.

A prime example is the discovery of strikingly similar obesity genes in rodents and humans--genes that may hold the key to appetite and weight. These genetic studies have led to the discovery of the hormone "leptin," thought to be a pivotal regulator of both appetite and energy utilization. The hormone leptin is produced in fat cells, circulates in the blood stream, and binds to receptors in the brain. This interaction then regulates a complex network that controls both satiety and food utilization. Mutations in the gene for the hormone leptin clearly cause obesity in rodents, and this information has already permitted early human studies. Most important from this example, however, is the rapidity in the progress of discovery from the gene defect, to the hormone, to the biotechnology of production of leptin--a seminal research tool and possibly an important prototype of pharmaceuticals useful in the treatment of obesity.

The progress I am describing today is the culmination of decades of basic research, as well as a specific obesity initiative NIDDK launched over four years ago, in anticipation of the importance obesity would attain both as a public health problem and as a research opportunity. We recognized then that we had an unprecedented chance to apply the new tools of molecular biology to stem the epidemic of obesity, which today affects one third of Americans. Within available resources, we rapidly pursued the use of genetic techniques to solve the puzzle of obesity. Our ultimate goal is to prevent the onset of obesity, which is a major risk factor for non-insulin-dependent diabetes and many other serious health problems. Along the way, we established a National Task Force on the Prevention and Treatment of Obesity to gain advice from eminent scientific experts; we funded four new obesity/nutrition research centers--one of which made the leptin discovery--and we established a new information-based outreach program. We also incorporated within our institute

the NIH Division of Nutrition Research Coordination to better integrate trans-NIH nutrition research and bionutrition initiatives. Now, we must sustain our research momentum, which is particularly important to minority populations, many of whom have very high rates of obesity and diabetes. For example, the Pima Indians of Phoenix, Arizona, are the focus of long-term NIDDK research aimed at understanding why they bear such a high burden from these closely linked diseases. Using this intensely studied population, NIDDK intramural and extramural scientists have joined forces with industry to mount the largest genetic search ever undertaken to find clues to the cause of both non-insulin-dependent diabetes and obesity.

Capitalizing on research opportunities has led to similarly impressive advances in combating cystic fibrosis, the most common fatal genetic disease in Caucasians. A diagnosis of cystic fibrosis was once a childhood death sentence. Today, CF patients survive well into adulthood, and the quality of their lives has been significantly improved. These dramatic changes are the result of long-term basic and clinical research. Most recently, the cloning of the CF gene and identification of its protein product have provided a revolutionary opportunity to understand this disease as a molecular abnormality. The demonstration that insertion of a normal CF gene can correct the chloride transplant abnormality in laboratory animals has made CF a prime target for research on potential gene therapy. A major focus of this research is the development and testing of different types of vehicles for transferring a normal CF gene into the body. While the very new technology of gene therapy remains our ultimate goal, we have not lost sight of the need to continue to develop more effective therapies to treat today's CF patients. For example, ibuprofen, a nonsteroidal anti-inflammatory drug widely used for arthritis, has been shown to slow the rate of lung-function loss in CF significantly. In other NIDDK-supported research, we studied three methods of removing mucous from the lungs. A device that aids chest physical therapy was found to be an effective, easy-to-use, inexpensive, portable device that can significantly increase the independence of patients with CF, reduce health care costs and improve treatment compliance.

By deploying the power of new molecular tools to define genetic and metabolic disorders, we also have made pivotal discoveries about the cellular receptor for one class of oral diabetes drugs, called the sulfonylureas. Building on over ten years of NIDDK-funded basic research, NIDDK grantees cloned the sulfonylurea receptor, called SUR, from hamster cells and demonstrated that it is a member of the growing family of signaling proteins, called ATP-binding cassette proteins, which also includes the protein responsible for cystic fibrosis. Related studies suggest that mutations in the SUR gene result in excessive insulin secretion and hypoglycemia in infants. This discovery offers new opportunities for research relevant to both hypoglycemia and diabetes.

Another example of advances flowing from exploitation of opportunities is the discovery of the gene for polycystic kidney disease (PKD). This

achievement was made possible by the advent of new techniques in cell biology and genetics. With the gene in hand, we have already elucidated its product--the protein "polycystin." We now have the opportunity to find the function of this protein and how the mutated, abnormal form causes PKD, a disease responsible for up to eight percent of end stage renal disease. These discoveries open new opportunities for therapeutic targets, as we move toward our ultimate long-range goal of gene therapy.

Our long-standing commitment to pursue opportunities in the basic sciences also has enabled us to undertake major new clinical trials of exceedingly high importance to the health of the American people. Moreover, it has spurred the U.S. biotechnology industry to develop new drugs, with economic benefits for the nation. Let me give you just a few examples on both fronts. In diabetes, advances in genetics and diagnostic techniques have enabled us to predict whether non-diabetic siblings of insulin-dependent diabetic children will develop diabetes. With this knowledge, it has been possible to design a major clinical trial to determine if the prophylactic use of either injected or oral insulin can prevent or delay the onset of the disease and thus forestall its devastating and extremely costly eye, nerve, kidney and cardiac complications. Similarly, a solid foundation of research on nutrient metabolism, energy expenditure, oral diabetes drugs, and methods for measuring impaired glucose tolerance has enabled us to design a clinical trial aimed at preventing non-insulin-dependent diabetes in high-risk individuals. Another example is urologic diseases, where the fundamental discovery of enzymes that regulate prostate growth has aided the pharmaceutical industry in developing medical therapies for benign prostate enlargement and has permitted us to design a clinical trial to test the relative efficacy of two of these drugs. Through this trial, we also hope to gain new insights into different types of prostate disease, including chronic prostatitis, as well as clues about normal and malignant prostate growth. In this regard, we have a close working relationship with the National Cancer Institute, with whom we fund three George O'Brien Urological Research Centers aimed at understanding benign prostate disease and prostate cancer, including genetic differences that might account for higher rates of prostate cancer in minorities. In all of these clinical trials, we have forged important collaborations with industry that have enhanced our resource base, but would not have been possible without an NIH initiative.

The return also has been great from our investment in basic research in hematology. For example, our research led to the biotechnology industry's ability to genetically engineer, produce and market a drug called erythropoietin or "Epo" for short. This is a growth factor for red blood cells that has proven enormously beneficial in treating the anemia of end-stage renal disease and AIDS. Moreover, it is beneficial in treating sickle cell anemia when combined with hydroxyurea, a drug pioneered by our intramural scientists for reducing the frequency of painful crises in adults with this disease. In addition,

molecular approaches to drug development have resulted in the discovery and production of thrombopoietin--a powerful growth factor for blood platelets, which we expect will also have an enormous impact on the biotechnology industry.

Cost-saving health benefits have emerged from the discovery that duodenal ulcers are associated with a bacterium, *H. pylori*, which can be easily and inexpensively eradicated by drug therapy. It has been estimated that \$400-\$800 million annually can be saved by preventing ulcer recurrence alone. By studying the molecular genetics and bacteriology of *H. pylori* infections, we are gaining insights about the relationships between specific virulence factors and disease. Now we know that people infected with *H. pylori* in early life are more likely to develop gastric cancer and gastric ulcer. Also, those with a particular strain of *H. pylori*--called the CagA gene type--are at risk for developing gastric cancer or duodenal ulcer. The CagA gene is present in 60 percent of *H. pylori* strains. These findings will pave the way to new opportunities for intervening in or preventing these chronic diseases.

Clearly, basic research yields enormous benefits. This is why we continue to invest in the neurosciences, and will exploit the recent discovery of a new hormone, urocortin, which might play a role in a wide range of inflammatory and behavioral health problems. This is why we will continue to support basic intramural research on structural biology, to disclose the three dimensional architecture of molecules important in diseases ranging from AIDS to cancer. This is why we will fund basic studies of bone metabolism that are vital to understanding diseases such as osteoporosis, as well as fundamental studies of growth factors and hormones that may play a key role in breast and prostate cancers. Similarly, we will maintain a strong commitment to developing transgenic animal models to give us clues about a wide range of diseases. For example, such a model for inflammatory bowel disease (IBD) is revealing the careful balance of pro-inflammatory and anti-inflammatory cells that is maintained in the normal intestine and disturbed in this disease. We are also sustaining our initiative on basic research on women's urologic disorders, including interstitial cystitis and incontinence. We believe that today's portfolio of basic research is the wellspring for the clinical trials, drug development, and health-care improvements of the future.

With your encouragement, Mr. Chairman, we have also launched new outreach programs to provide the American people with science-based information that directly affects their health needs. Our new "National Diabetes Outreach Program" is conveying the positive message from a ten-year multicenter NIDDK clinical trial, which showed that patients with insulin-dependent diabetes can prevent or greatly reduce the eye, kidney and nerve complications of diabetes by maintaining their blood glucose levels as close to normal as possible throughout the day. Our slogan for this effort is "DO YOUR LEVEL BEST." Another new outreach effort is our "Weight-Control Information Network," or WIN. Callers to our 1-800 numbers for each of

these programs can hear a pre-recorded message and obtain science-based written information. The WIN program is also pilot-testing a health information message to inner-city African American women in Boston, Massachusetts. The message is, "SISTERS TOGETHER: MOVE MORE, EAT BETTER." Both these outreach programs represent very important efforts to complement our biomedical research portfolio by bringing its findings to the American people.

Mr. Chairman, today, I have presented just a few examples of how NIDDK has used its resources to exploit research opportunities in the basic sciences. This approach has paid off in achieving major advances to benefit our citizens; in enabling the design of important clinical trials; and in contributing to the U.S. biotechnology and pharmaceutical industries, often with positive economic effects. I hope these examples convey the excellence and productivity of NIDDK basic research and the exponential effects that can be realized by our investments in fundamental sciences. The Fiscal Year 1997 budget request for the NIDDK is \$772,975,000.

Phillip Gorden, M.D.

Director, National Institute of Diabetes and Digestive and Kidney Diseases

December 22, 1934. Baldwyn, Mississippi. Married, two children.

Education: B.A., Vanderbilt University, Nashville, Tennessee, 1957;

M.D., Vanderbilt University School of Medicine, Nashville, Tennessee, 1961.

Professional History: 1961-62, Intern, Yale University, New Haven, Connecticut. 1962-64, Assistant Resident, Yale University, New Haven, Connecticut. 1964-65, USPHS Clinical Fellow in Metabolism, Yale University, New Haven, Connecticut. 1965-66, USPHS Research Fellow in Metabolism, Yale University, New Haven, Connecticut. 1966-74, Senior Investigator, Clinical Endocrinology Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. 1974-78, Senior Investigator, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1974-76, Clinical Director, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. 1976-78, Visiting Professor, Institute of Histology and Embryology, University of Geneva School of Medicine, Geneva, Switzerland. 1978-present, Chief, Section on Clinical and Cellular Biology, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1980-1986, Clinical Director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1983-1989, Chief, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1986-present, Director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Professional Organizations: American College of Physicians, American Diabetes Association, American Federation of Clinical Research, American Society for Clinical Investigation, Endocrine Society, American Society for Cell Biology, Association of American Physicians, American Society for Biochemistry and Molecular Biology.

Honors, Awards: Alpha Omega Alpha Medical Fraternity, 1961. Doctor of Medicine (Honoris Causa) - University of Geneva, Geneva, Switzerland, 1986. Public Health Service Distinguished Service Medal, 1986. Public Health Service Commendation Medal, 1988. Distinguished Alumnus Award and Medal, Vanderbilt Medical School, 1990. Istituto Rotariano per l'Italia Meridionale (IRIM) Award of the Rotary International, Naples, Italy, 1992. Public Information Award of the Juvenile Diabetes Foundation, International, 1992. National Scientific Leadership Award, Crohn's and Colitis Foundation of America, Inc., 1993. Public Health Service Surgeon General's Exemplary Service Medal, 1993. David Rumbough Award for Research, Juvenile Diabetes Foundation, International, 1994.

LEPTIN AND THE OBESITY GENE

Mr. PORTER. Thank you, Dr. Gorden.

Ms. Pelosi, I think we'll go on five minutes, because we don't know who's going to be here, and we'll go back and forth if other members don't arrive.

You talked about the hormone produced by fat cells, leptin. And I wonder if you can make some sense out of the press stories on this, Dr. Gorden. First it seemed that obese lab animals had a shortage of leptin, which sent drug companies off to try to produce leptin as a weight loss therapy. Then other researchers showed that most overweight people have an excess of leptin in their blood.

Where does that leave the obesity research community in its search for weight control medications?

Dr. GORDEN. Everything you say is fundamentally true, Mr. Chairman. I think that this is an emerging field, and we are at a very early stage of our understanding. And it's easier sometimes to use analogies of things that we have studied and understand over a longer period of time. And the analogy that I would use would be non-insulin-dependent diabetes, where it was assumed that there was a deficiency of insulin. It turns out that for most non-insulin-dependent diabetics, there is no deficiency of insulin. There is a resistance to insulin.

And so if I were to draw an analogy, I would say that we would have not predicted that we would have found the genetic mutation in the rodent which leads to the disease, the deficiency of the hormone which leads to the disease in man. And that we more likely, if this analogy holds, would find a resistance.

Now, it is true that insulin is in fact a treatment for all forms of diabetes, regardless of what the cause. And there are many different causes of diabetes. By analogy, again, it's very early and very preliminary, but by analogy, we might assume that leptin, even though it's not deficient, and though it might even be present in excess in certain obese patients, might still be used for the therapy of obesity or some type of leptin-like drug, might be used for the therapy of obesity analogous to what we do today for non-insulin-dependent diabetes.

Mr. PORTER. But we don't know that either, yet?

Dr. GORDEN. We don't know that. That's exactly correct.

DIABETES PREVALENCE

Mr. PORTER. You're researching that.

We understand that the prevalence of diabetes, speaking of diabetes, is up 50 percent since 1983. Is this the result of demographic changes in aging, an overweight population, or is there something more at work here?

Dr. GORDEN. We are unable to detect any other trend. It appears to be a change in population demography, of higher risk populations in our country. It appears to be related to an aging population, in which diabetes is more prevalent. Certainly, the non-insulin dependent form is the most prevalent form of diabetes. And this is what we see essentially increasing.

So we don't believe there's any other factor. It is related, we believe, to all the things that you've mentioned.

DIABETES CLINICAL TRIALS

Mr. PORTER. Recent reports indicate that diabetes is the country's most costly chronic disease, accounting for more than \$92 billion per year in health care costs alone. In your view, what are the most promising leads to finding a cure or prevention for diabetes?

Dr. GORDEN. I think we've come a very long way in understanding both of the general forms of diabetes. This has involved a large number of very basic, fundamental discoveries over the years. We now know that insulin dependent diabetes is an immunologic disease. And we have to pursue treatment by methods to control or interdict the immunologic process. We know that non-insulin-dependent diabetes is a metabolic disease, that is, it's related to altered body metabolism—a totally different process.

We've learned an awful lot about the sequence of events from the very earliest point in both of these diseases to the final point where the disease is expressed. This gives us an opportunity now, for the first time, to actually try to prevent both of these. And we've in fact launched clinical trials in an attempt to interdict the full manifestation of the disease in each case in a primary prevention trial. This is really the first time this kind of effort has ever been undertaken.

So we think that by actually having the ability to do studies like this that we have really learned a great deal, and acquired a great deal of knowledge in order to bring these types of studies about.

DIABETES—GENETIC BASIS

Mr. PORTER. The committee began to indicate its interest in the search for the genetic basis of diabetes, both the juvenile and adult onset form, several years ago. What is the status of that effort?

Dr. GORDEN. Again, in both forms of diabetes, we feel that there is a genetic component. There is another component, but clearly there's an important genetic component. In the insulin-dependent form of diabetes, we clearly have defined a number of what we call loci. In other words, regions of the entire genome where important genetic contributions to diabetes occur. We don't know precisely what the genes are, but we know that they are important areas in which to continue to look.

In the noninsulin-dependent form, the same kind of thing is beginning to emerge. We now have a number of examples of both what we call candidate genes, that is, genes that we would choose to study to see if they might be related, because we know they are likely to be related. And also, we've done it the other way around, by taking a purely genetic approach and trying to find causes. In both cases and in both forms of the disease, there's clear progress.

There's no question that in these so-called polygenic diseases, that is, diseases that clearly have more than one gene involved in producing the full manifestations of the disease, that it's much more complicated, much more difficult, than it is in the so-called monogenic diseases, such as cystic fibrosis and others, where we find a single gene and we clearly have the etiology of the disease. That's not true in the complex diseases. We think diabetes research has moved clearly as far as any of the complex genetic disease re-

search has so far. So we've been pleased, but we still have a great deal more to do.

Mr. PORTER. Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman.

Dr. Gorden, welcome. Thank you for your testimony.

Dr. GORDEN. Thank you.

DIABETES PREVALENCE

Ms. PELOSI. Following up on our Chairman's question about the 50 percent increase, could you, if you mentioned this in your statement while I was out of the room, forgive me for asking this, could you comment on how much of this might be juvenile onset diabetes, or juvenile diabetes, or not?

Dr. GORDEN. Yes.

Ms. PELOSI. We hear so much from our constituents on that subject, and so many people even in my own office are affected by that.

Dr. GORDEN. The so-called juvenile form, or what we refer to as Type I or insulin-dependent diabetes, accounts for about 10 percent of the total number of diabetics. The non-insulin-dependent form accounts for approximately 90 percent. Again, the increase appears to be in predominantly the non-insulin-dependent form, where again, we believe that this is due largely to changes in population demography and also to an aging population, rather than some systematic event that's occurring that would actually increase the incidence of the disease.

Ms. PELOSI. So the impact is not so much on juvenile diabetes?

Dr. GORDEN. Not so much with respect to the increase. There are clearly many more Type I diabetics, because their life expectancy has been improved, and the issues related to their care are becoming greater in the sense that there are many more people. So they do account for this increase in prevalence, just as in the non-insulin-dependent form. It's just that the larger number comes from the non-insulin-dependent form.

DIABETES CLINICAL TRIALS

Ms. PELOSI. Dr. Gorden, can you tell us more about the ten year multi-center diabetes clinical trial, what have been the major findings and how are these findings being used to improve the quality of life for diabetics?

Dr. GORDEN. We actually have two trials. The first I believe you're referring to is the diabetes prevention trial for non-insulin-dependent diabetes. This trial will involve approximately 4,000 people. It's beginning its recruitment now. It will involve tests of lifestyle changes to determine whether things like diet and exercise and other types of lifestyle changes can be used to actually prevent the overt diabetes attack.

It will also include at least two drug arms. We will use a particular point we call impaired glucose tolerance, which is a phase that we can actually measure during which we know the risk of diabetes is very high. We have to use this marker as an actual starting point for the clinical trial and our end point will be diabetes.

This trial is now beginning. We have no actual results from the study at this point in time. But all of the protocols have been ap-

proved and all the centers have been established. We are basically ready to go at the moment the study is fully inaugurated.

Ms. PELOSI. So this is about prevention and control and management?

Dr. GORDEN. This is about primary prevention. In other words, we will take individuals who do not have diabetes, but who are at high risk for developing diabetes, and determine whether we can actually prevent or delay the disease. Either one will be very important. Because at any point that we can delay the onset of hyperglycemia—high blood sugar, which we know is essentially a type of toxin in the diabetic patient—that will be a benefit to the patient over a lifetime.

Ms. PELOSI. Do you have another trial going?

Dr. GORDEN. Yes, we have a trial in the insulin-dependent form, the juvenile form, because we can now recognize the immunologic markers of the disease before the disease itself is manifest. And we can recognize those markers as early as five years beforehand, or even earlier than that by simply measuring a blood test and using other parameters to decide whether that individual is at high risk. We can then intercede by a mechanism in which we try essentially to trick the immune system, very much like a vaccination tricks the immune system, to try to prevent this attack on the insulin producing cells.

That study is actually further along. It's been going on for a longer period of time. We screened approximately 70,000 patients, which illustrates the enormous interest in the trial. Networking has proved highly effective in bringing people into the screening for the trial. About 70 people have actually been recruited and are in the first phase of this trial now.

DIABETES—GENETIC BASIS

Ms. PELOSI. Well, Dr. Gorden, may I just ask, how do you determine who you give this blood test to? Are you suggesting all children should have it, or people with a genetic situation?

Dr. GORDEN. You've hit upon a very important area. About 15 percent of insulin-dependent diabetes occurs in families, so it is there that we go first. We know that the incidence rate for a second child in a family with known diabetes is higher, and that is where we do our selection. At the present time, we have to select those individuals that are screened for this clinical trial out of families with a diabetic child or a diabetic parent.

Ms. PELOSI. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Gorden, nice to see you again.

Dr. GORDEN. Thank you, Mr. Stokes.

LEPTIN AND THE OBESITY GENE

Mr. STOKES. Doctor, obesity is a major factor in a number of diseases and disorders. And in this past year, there's been a great deal in the media about the genetics of obesity discoveries funded by your Institute. How critical is this obesity gene research to im-

proving the health of the American people, and which major diseases and disorders would benefit from additional research in this area?

Dr. GORDEN. Mr. Stokes, obesity is certainly an extremely important problem in the United States. Approximately a third of our population is actually obese and subject to increased risk of a variety of types, both cardiovascular and diabetes. So obesity is a very important risk factor for a number of major health problems that we face in this country.

What's been discovered in the last year, and I was speaking of it in my opening statement, is the hormone leptin, which is a derivative of a genetic mouse. We now actually have identified this hormone from patients. The most important thing is that we now have an opportunity to understand this system in a more central way. That is, we have an opportunity to understand the central mechanism by which both appetite and energy utilization are controlled. So that's been a very key, important discovery.

It doesn't mean that at the present time, for the control of obesity, we don't have to rely on many of the kinds of things that we have in the past, and many of the approaches that we've taken. But clearly research in obesity is going to have enormous consequences with respect to diabetes, with respect to cardiovascular disease, with respect to gallstones, and with respect to a whole host of other problems which are known to be enhanced by the presence of obesity.

PROSTATE DISEASE RESEARCH

Mr. STOKES. Doctor, moving to another area, the fiscal year 1996 appropriations bill included language directing the Urology Interagency Coordinating Committee to develop a plan to address the problem of prostate disease in minorities. What progress has been made in the development of future plans for action in this area?

Dr. GORDEN. We have, first of all, just signed a memorandum of understanding with Dr. Klausner and the National Cancer Institute to sort of reaffirm our cooperative agreement in the study of prostate disease. We have a lot of interacting grants, and centers that we co-fund. There are a number of agreements that we want to reaffirm since he has become the new Director of the Cancer Institute.

Second, we have issued requests for applications for basic research in prostate growth, which clearly is going to be very important. Third is that we have just inaugurated a major clinical trial, which is making a special effort to recruit minorities to interdict the problem of benign prostatic hypertrophy, which is a major problem as we deal with an aging population.

So at least in those three areas, and a number of others, we clearly have a plan and a very clear approach to the problem.

PROSTATE CLINICAL TRIAL

Mr. STOKES. Are there plans to do clinical trials in this area?

Dr. GORDEN. We certainly are involved in the clinical trial of benign prostatic hypertrophy. And we have been interacting with the National Cancer Institute as they pursue a variety of trials that relate to prostate cancer.

Mr. STOKES. Great. Mr. Chairman, how much time do I have remaining?

Mr. PORTER. You still have a little time.

GENETIC BASIS OF DISEASES

Mr. STOKES. Okay, thank you. Just let me know when I've exceeded my time.

Doctor, what's the association of genetic predisposition with diseases and disorders under the purview of your Institute?

Dr. GORDEN. In regard to genetic predisposition, certainly there are a whole host of diseases in the Institute. Diabetes, as we've discussed, has an important genetic predisposition. Obesity, as we've discussed, has an important genetic predisposition. There are a whole host of rare diseases that we are involved in, and certainly sickle cell disease has a genetic predisposition.

There are a whole host of metabolic rare diseases that have genetic predispositions, and a variety of gastrointestinal diseases that have genetic predispositions, including inflammatory bowel disease. And certainly, in the kidney area, diseases like polycystic kidney disease are all genetic and there are many others. So right across our Institute is a whole host of individual diseases, all of which have genetic predisposition.

Mr. STOKES. Thank you, Dr. Gorden.

Thank you, Mr. Chairman.

RESEARCH PROJECT GRANT NUMBERS

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Gorden, the mechanism table for your non-AIDS budget indicates that the number of competing grants will rise from 438 in 1996 to 640 in 1997, a 46 percent increase. I realize that you may have to conform to overall NIH goals about the number of new grants in 1997, but would you prefer to increase the inflationary increase given to grants rather than to raise the number of new grants and build in out-year costs?

Dr. GORDEN. One of the reasons that it's important for us to increase the number of grants is because in 1996, we will have a lower number than the usual number of competing grants. So we come off a low year onto a year that increases.

For us, the issue of increasing the number of grants is going to be very important. It is difficult to draw an exact line at this point in time, as to where we would actually prefer to be. But we're comfortable, certainly, increasing the number of grants, as you see here, by approximately 200. The 640 number is a very comfortable figure for us.

PROSTATE DISEASE RESEARCH

Mr. PORTER. We received public witness testimony this year describing the problem of prostatitis. The witness said very little is known about the treatment for the disease, and asserted that 50 percent of men are affected. Can you comment on this testimony and tell us what your Institute is doing in this area, and do we have any clues about the cause of the histologic lesion causing prostatitis?

Dr. GORDEN. We have a very significant and large prostate disease program. Within that program, we address problems that generally relate to the causes of prostatitis. But there is clearly always the potential for gaps in that program, and areas that are not being fully addressed.

We recently brought together a group of people to advise us on this point. It turns out that the term prostatitis is a generic term that refers to a large number of possibly different conditions that produce pelvic pain. This was the conclusion of the group. Their major advice to us is that we must clearly define what we're calling prostatitis in order to inaugurate new types of approaches to this problem.

That's exactly what we plan to do. We plan to define a subset of these conditions, so that we can really define a useful research plan. So we have this task before us, we've had our meeting with the experts, and we're in the process of formulating a mechanism to define a research plan.

INTERSTITIAL CYSTITIS

Mr. PORTER. The committee has registered its interest in the problems of female urology, especially interstitial cystitis. Could you tell us what research initiatives are underway, focusing on women's urologic conditions, and if there is any collaborative work with the Office of Research on Women's Health?

Dr. GORDEN. This is again another example where we really had to start at a very basic level and build a program. I think that this field has really shown an enormous amount of promise over the last several years. It has had two components.

The first component was to try to understand the basic physiology of the bladder, of which there is very little known, and the basic pathophysiology of the bladder, of which there is even less known. We then established a database in which we began to recruit patients, so that we can actually define Interstitial Cystitis, and we can begin to use clinical materials to enhance the basic studies that are being done.

This has, I think, proven quite successful. The Office of Research on Women's Health—ORWH—has been quite interested in this program, and this year they will have the largest involvement in this program. We've just culminated an agreement for fiscal year 1996 funding, in which the ORWH has expressed special interest in this particular area, and we expect an excellent cooperative effort with that office in carrying out this program.

We're also in the process of actually determining what is the most effective way to recompute the Interstitial Cystitis database, which we think is a very useful part of the research program, and we would like to extend the database's support, perhaps in a slightly different focus. But all the plans for this are presently in the works.

POLYCYSTIC KIDNEY DISEASE

Mr. PORTER. Advocates for PKD research contend that it is a neglected field, considering the number of patients affected and the financial burdens of the disease. First, do you agree with that characterization, and secondly, we understand that there have been

some major advances recently in research into PKD. How do you plan on capitalizing on these research opportunities?

Dr. GORDEN. Well, I think this is really one of the excellent examples of the pursuit of research opportunities. We have built a program that in fiscal year 1996 will approach approximately \$7 million in this particular area alone. This represents a very significant growth in the program over the last three or four years. Out of this has come the discovery of the gene for PKD, and out of it has come the discovery of the gene product, and clearly, that is an opportunity.

This year we pursued the question: "what does this gene product do, what does this protein do, how does it produce polycystic kidney disease?" We clearly have the opportunity to understand that answer, and it is something we need to pursue vigorously. We actually have a set of proposals that we plan to fund this year.

Just as news of this discovery began to break, we began to solicit applications to pursue this exact area. So I think it's one of the very good examples of pursuing opportunity. I would never argue with any group that says they're underfunded. Certainly, there are many areas in our Institute that feel that they are underfunded.

On the other hand, I think we've made significant progress and I think the growth in that particular program has been rather remarkable over the last three to four years, to the point where we now have approximately a \$7 million program in that area alone.

Mr. PORTER. Thank you, Dr. Gorden.

Ms. Pelosi.

HELICOBACTER PYLORI

Ms. PELOSI. Thank you, Mr. Chairman.

I have one question. Dr. Gorden, in your written statement, you say cost saving health benefits have emerged from the discovery that duodenal ulcers are associated with a bacterium *H. pylori*, which can easily and inexpensively be eradicated by drug therapy, and it is estimated that \$400 million to \$800 million annually can be saved by preventing ulcer recurrence alone.

Following up on your comment, it is my understanding that researchers from the Centers for Disease Control and Prevention who are looking for a dietary explanation for anemia among Alaskan Natives found nearly a universal infection with *H. pylori*. What is being done to diagnose and treat this disease? Is your Institute working with the CDC on this issue?

Dr. GORDEN. This is one of the excellent examples of where we have taken a chronic disease, duodenal ulcer, and converted it to an acute disease, so that it can be treated over a short period of time, let's say, two to three weeks, rather than a lifetime. This advance is really what accounts for these cost saving figures that you've just quoted.

We have taken advantage of the basic research. We've had a consensus conference which really at the time catalyzed this whole strategy of treatment and allowed us to move forward. In the past week, the FDA has approved a combination drug regimen for the treatment of helicobacter. Now we're moving into an area where I believe much more can be accomplished.

We have always had many interactions with the CDC, and we're very interested in the epidemiology of helicobacter infection. We're not quite sure at this point what to do about the broad epidemiology of helicobacter. So we've focused primarily on the duodenal ulcer and some of the basic issues and also the issues that relate to gastric cancer. We also have an interactive program that we're discussing with at least three other institutes about how to pursue the research and approach this health problem.

DIABETES RESEARCH

Ms. PELOSI. I just have one final question, Dr. Gorden. But there was in the news about a month ago a report that there was a cure for diabetes. Did you ever hear that? It didn't obviously go on to say what it was, just said that they were hopeful and there was this cure and this advance had been made. Is that, did you ever get wind of this press report?

Dr. GORDEN. Unfortunately, I get wind of such reports far too often, Ms. Pelosi. It's one of the unfortunate things, where sometimes a discovery will be reported and it will essentially go beyond what the discovery really means. We don't have a cure for diabetes, there's no question about that. We have some very important findings that we hope are leading us to some interdictions and possibly to prevention.

We don't really even know what form a cure is going to take. A cure can take a variety of forms. A cure in polio took the form of prevention. A cure in duodenal ulcer is going to take a different form. We're not really quite sure, but we're beginning to focus on what we can do, that is, prevent some of the complications of the disease. The Diabetes Control and Complications Trial had an enormous effect on showing what control of the blood sugar can do. Is that a cure? No, but it is a very beneficial approach.

So we're presently faced with important approaches, and deciding which ones are going to be the most important is what our challenge is. It is unfortunate that sometimes discoveries get expressed in ways that are not entirely accurate. I think the report that you refer to would be an example.

Ms. PELOSI. Was there some anecdotal information that emerged?

Dr. GORDEN. I don't really know exactly what—

Ms. PELOSI. It's not a fair question to you, but I just wondered, from the chronology of it, if there was anything that you could identify. But I don't have enough information, obviously, if it was just one news report, and then not much following it. But Dr. Fauci was telling us earlier how he doesn't like to call anything a breakthrough, because sometimes it takes wing, and people have expectations that are not there. And I didn't know what the basis for the news report was.

For example, this morning, Mr. Chairman, I was leaving home, I heard just the end of a news report that there was a big breakthrough in breast cancer. When I met with the head of the National Cancer Institute this morning, it again was some anecdotal information that did not justify the kind of report, my impression is it did not justify the kind of report that it was being given on the air.

In any event, I thank you for your very serious work. Forgive my question at the end, which was not scientific. And thank you for your time.

Dr. GORDEN. Thank you very much.

Mr. PORTER. What kind of publication was that in, Ms. Pelosi?

Ms. PELOSI. It was on the airwaves. And I figured, oh, tomorrow, I'll read all about it in the paper. And of course, that never appeared.

Mr. PORTER. Some of our media is getting closer and closer to the National Enquirer standards of journalistic reporting, I'm afraid.

Ms. PELOSI. I don't even know if they were attributing it to divine intervention, which is something I believe in, too.

Mr. PORTER. We will have a third round. Mr. Stokes.

HELICOBACTER PYLORI

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Gorden, you may have heard Dr. Fauci's response when I asked about gastric cancer and peptic ulcer this morning. I notice in your opening statement that you, too, have done some research in this area. To what extent is there collaboration between your Institute and Dr. Fauci and his institute on this research?

Dr. GORDEN. We have, at the present time, a discussion relating to H. pylori both with the National Cancer Institute and Dr. Fauci's institute and also the National Institute of Child Health and Human Development, about further approaches to this question. The link to gastric cancer is one that has been suggested although it has not been proven. It is also interesting that the incidence of gastric cancer has been dropping in this country.

The reason for that is not entirely clear, but there is some speculation that it might possibly relate to treatment of helicobacter. Again, I would couch that in very cautious terms. But it is fair to say that these are the kinds of clues and the kinds of approaches that we need to be following up. Because if that's in fact true, that would be an extremely important observation for us to pursue.

We are beginning that follow-up, and we are doing it in a collaborative way. Because each of the institutes have very specific interests. We in NIDDK have a major interest in gastroenterology and peptic ulcer. Dr. Fauci's institute has an interest in infection, the Cancer Institute's interest is obviously infection and cancer, and in the Child Health Institute, it is the relationship of this disease to children. So we do have a lot of mutual interests.

DIABETES IN MINORITY POPULATIONS

Mr. STOKES. Doctor, minorities are disproportionately affected by non-insulin dependent diabetes. Can you bring the subcommittee up-to-date on the Institute's clinical trial aimed at preventing non-insulin dependent diabetes?

Dr. GORDEN. You are quite correct, Mr. Stokes, certainly in all minority populations there is an increase in the prevalence of non-insulin-dependent diabetes. That is why, in this diabetes prevention trial, we are going to recruit at least 50 percent of our patients from minority populations, because they are the most vulnerable and because they are at the highest risk. And also, as I was pointing out earlier, because of the tremendous basic research that's

gone into this area, we now have an opportunity to do this trial. That's what's so important.

It's important that we direct the research at those who are the most vulnerable and that's exactly what we intend to do. The Type II trial is progressing extremely well, with the full recruitment expected to begin in the very near future. We're very optimistic about this being an important approach.

Let me just cite one example. We know that approximately 20 percent of individuals who we detect with non-insulin-dependent diabetes already have complications of diabetes when they are first detected. This is why it's so imperative for us to get ahead of that in time, to try to find if we can actually prevent the disease. This will have enormous ramifications for public policy related to diabetes screening and other preventive measures. But we've got to actually prove that we can accomplish some degree of prevention before we actually raise issues that relate to screening.

DIABETES CLINICAL TRAILS

Mr. STOKES. How much is included in your fiscal year 1997 budget for clinical trials?

Dr. GORDEN. For clinical trials altogether, or for this particular trial?

Mr. STOKES. Specifically, I'd like to know about this one.

Dr. GORDEN. This particular trial includes approximately \$14 million of our own contribution. We have enhanced that considerably by both industrial contributions and contributions from other institutes and also from the American Diabetes Association. So we've actually listened very closely to what you and the Chairman have told us about enhancing our own resources.

We've tried very hard in these clinical trials, to be the nidus in which others would like to join. It has been really extraordinarily gratifying to see how other organizations have now joined in this effort. There are several. This will enhance the trial by another several million dollars over and above our contribution.

MINORITY HEALTH PROBLEMS

Mr. STOKES. Let me pose a question to you that you may have heard me pose to Dr. Fauci. I have of course posed it to you and other institute directors over the years as well. My concern is about the overall gap between minority health and majority health in our country. I think all of us acknowledge that this is a very serious problem, and one that we need to make greater progress on. From the perspective of your Institute, can you tell us whether we're making any meaningful progress or not?

Dr. GORDEN. Well, I think that the progress can be measured by the numbers of things that we're doing in the areas of obesity, diabetes, and hypertensive kidney disease. These are three really important areas, and we have extremely important collaborations with the Office of Research on Minority Health. This fiscal year, we will have at least a \$7 million contribution from that office alone.

Our ability to address these problems and our ability to recognize, for instance, the vulnerability of African-Americans to hypertension, with respect to the kidney, followed by our ability to rather rapidly introduce a clinical trial to address this, speaks to the

kinds of actions that you're talking about. These research efforts clearly are going to have a major effect on these health problems. They must then eventually have an effect on this gap that you refer to.

You appropriately continue to remind us of this gap, and we're very mindful of it. We must approach that by trying to address research to each problem directly with the full notion that research findings are going to have an important effect on this gap that you speak of. I definitely believe they will.

Mr. STOKES. Thank you very much, Dr. Gorden. I know that you're concerned. We just have to continue to make progress in this area that all of us are very much concerned about. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

POLYCYSTIC KIDNEY DISEASE

Dr. Gorden, we are being encouraged to direct you to fund PKD research centers. We try to stay away from dictating particular research mechanisms, deferring to the scientific judgment of the institutes. What is your view of establishing a network of PKD research centers within your current resource pool?

Dr. GORDEN. Well, we have a variety of ways to fund and support PKD research. My own view is that mechanisms such as grants will be a far more versatile and effective mechanism than centers at this point in time for this disease. Now, that may not be true at some other point in time. But in my own view, at this point in time, we will be much more effective if we're able to use the grant mechanism than a center mechanism.

RESEARCH CENTERS POLICIES

Mr. PORTER. Dr. Varmus, could you describe for us how decisions are made about the number of research centers NIH supports? Is a cap set centrally on the total number of centers and the dollars allocated to this mechanism? Or is this an individual institute decision?

Dr. VARMUS. Well, both, Mr. Porter. As you know, in general, we leave the number of centers and the amount of money devoted to centers within each Institute Center and Division up to the directors, because we feel that the appropriateness of the center mechanism does vary dramatically among the institutes.

This year, as you know, because of the constraints upon our budget proposal, we have directed that there would be no increase in funding for centers this year. That doesn't mean that individual institutes might not increase by small numbers or decrease by small numbers the number of centers that they have. But the intention is to keep a cap on the center mechanism for this current year to allow us to fund as many investigator-initiated grants as possible.

Mr. PORTER. Mr. Stokes, do you have any final questions?

Mr. STOKES. Mr. Chairman, I have a few additional questions, but I'll be glad to submit them for the record.

Mr. PORTER. All right, thank you, Mr. Stokes.

Dr. Gorden, we thank you for your good testimony today. You're doing a fine job there, and we very much appreciate your coming before the committee and enlightening us.

Thank you so much.

Dr. GORDEN. Thank you very much, Mr. Chairman.

Mr. PORTER. The subcommittee will stand in recess until 1:30 p.m.

[The following questions were submitted to be answered for the record:]

POLYCYSTIC KIDNEY DISEASE

Mr. Porter: It has been estimated that dialysis costs in 1995 were in excess of \$11 billion. What does it cost the Federal government annually for PKD's portion of this total dialysis expense and for kidney transplants due to PKD?

Dr. Gorden: The United States Renal Data System estimates that in 1994 Federal and private payments for dialysis associated with ESRD due to cystic kidney disease totaled \$292 million. Of this \$292 million, Medicare paid \$228 million. Total Federal and private payments for kidney transplants attributed to cystic kidney disease were \$85 million, of which Medicare paid \$67 million. Other Federal medical costs totaled \$26 million. This figure includes payments for organ acquisition, HMO patients, and other unspecified medical costs. These costs may be slightly overestimated as available data refers only to "cystic kidney disease" and not all cystic kidney disease is PKD-related.

Mr. Porter: We have learned that NIDDK recently convened a special Scientific Conference on Polycystic Kidney Disease. Can you summarize the outcome of this meeting and what it means for PKD research?

Dr. Gorden: The Institute's ad-hoc PKD Advisory Committee recently held a workshop to examine the opportunities available for prospective PKD research. The Committee felt that there was an urgent need to study the association between different genetic mutations and the resultant clinical expression of PKD, the correlation between the severity of renal and non-renal conditions and the PKD genotype, the development of a standardized test for PKD, the development of animal and cell culture models to study PKD gene defects, and the definition of a model to use as a test for gene therapy as well as the determination of what genes should be inserted and how long they should be expressed. Other areas that need to be studied include the effect of associated conditions such as hypertension, race, and gender on the expression of PKD, pain management, the search for markers of PKD, the role of the PKD protein in cell-cell communication and cell signaling, and the pathophysiology of disease progression. These recommendations will be used to guide future research directions in PKD.

FUNCTIONAL BOWEL DISORDERS

Mr. Porter: Does your Institute plan any expansion of its clinical research and education activities with respect to functional gastrointestinal disorders?

Dr. Gorden: The Institute has issued a solicitation for small grants for clinical trials in digestive and nutritional diseases, including functional bowel disease. We expect a strong response to this initiative. In addition, NIDDK has just begun funding of large-scale clinical study of treatments for chronic, painful functional bowel disorders (FBD). FBD is a complex disease that predominately affects women. The cause of FBD is not clear, and therapies are limited in effectiveness. In this trial, the investigators will compare the cognitive-behavioral psychological treatment with antidepressant therapy and education/attention placebo in over 300 women. We have long recognized the interrelationships between psychological and physiological factors on the development and treatment of FBD. This large-scale study is designed to investigate interactions among physiologic measures, psychologic and sociodemographic factors, severity of symptoms, and therapeutic improvement, including quality of life. With scientific evidence to document the

efficacy of treatments of FBD commonly used in practice, clinicians would be provided with predictors of success among types of FBD patients and types of therapy that will improve symptoms and quality of life and at the same time reduce the health care costs associated with this common syndrome. This trial will be the largest and most comprehensive study of therapy for FBD ever conducted in the United States. As to educational activities, the Institute-supported National Digestive Diseases Information Clearinghouse will continue to provide a central point for the exchange of information among professional organizations, foundations, and voluntary health organizations involved with digestive health and disease. An informational packet on functional bowel disorders is available and is one of the most frequently requested materials. The Clearinghouse also provides information from a large national database of patient education materials.

DISEASE FUNDING

Mr. Porter: Identify 1995-1997 spending on the following: diabetes, interstitial cystitis, obesity, prostate, inflammatory bowel disease, celiac disease, osteoporosis, nutrition, cystic fibrosis, polycystic kidney disease, Cooley's anemia, sickle cell anemia, liver disease, prostatitis, and IgA nephropathy.

Dr. Gorden: The following identifies funding by the National Institute of Diabetes and Digestive and Kidney Diseases for the disease areas listed below in fiscal years 1995-1997:

	<u>1995</u>	<u>1996</u>	<u>1997</u>
Diabetes	\$193,597,000	\$202,700,000	\$205,500,000
Interstitial Cystitis	8,918,000	9,000,000	9,100,000
Obesity	34,200,000	35,700,000	36,100,000
Prostate	14,675,000	15,300,000	15,500,000
Inflammatory Bowel Disease	15,383,000	16,000,000	16,200,000
Celiac Disease	1,876,000	1,960,000	1,980,000
Osteoporosis	22,697,000	23,700,000	24,000,000
Nutrition	75,980,000	79,500,000	80,300,000
Cystic Fibrosis	21,670,000	22,600,000	22,900,000
Polycystic Kidney Disease	6,873,000	7,100,000	7,200,000
Cooley's Anemia	6,618,000	6,900,000	7,000,000
Sickle Cell Anemia	6,753,000	7,060,000	7,200,000
Liver Disease	46,200,000	48,300,000	48,900,000
Prostatitis	14,675,000	15,300,000	15,500,000
IgA Nephropathy	13,000,000	13,500,000	13,600,000

RESEARCH CENTERS

Mr. Porter: Identify the number and subject matter of research centers supported in FY 1996.

Dr. Gorden: The NIDDK supports a total of 59 research centers:

(1) Twelve diabetes research centers -- six Diabetes Research and Training Centers (DRTC), and six Diabetes-Endocrinology Research Centers (DERC). The essential difference between the two types of centers is that the DERCs focus entirely on biomedical research, while the DRTCs have an additional Demonstration and Education component. Examples of research that is being conducted at these

centers include investigations of the genetic basis of insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM); clinical physiology of insulin secretory alterations in subjects with different genetic forms of NIDDM; pancreatic islet physiology, chemistry, and molecular biology; carbohydrate metabolism; diabetes complications; analysis of insulin action on gene expression; and inhibition of fat breakdown by insulin in abdominal obesity.

(2) Five Cystic Fibrosis (CF) Research Centers, which focus on areas such as inflammation and host defense in the lung, clinical studies, epithelial cell biology, various aspects of the cystic fibrosis transmembrane regulator mutation and protein, and development of new treatments for CF.

(3) Three Gene Therapy Centers for Cystic Fibrosis and Other Genetic Diseases, which are investigating such areas of fundamental research as the development of safer and more efficient gene therapy vectors, development of animal models, and basic mechanisms of gene transfer.

(4) Twelve digestive diseases research centers, which focus on liver diseases and disorders, inflammatory bowel diseases, ulcer disease, gastrointestinal (GI) biology and hormones, and fundamental studies of the structure and function relationships in the digestive tract.

(5) Six Clinical Nutrition Research Units (CNRUs), which provide shared facilities and research services for studies in perinatal nutrition, nutrient transport, energy expenditure, hypertension, obesity, trace elements in nutrition, nutrient absorption, vitamin D metabolism, food intake, impact of alcohol on GI function, diabetes, hypertension and fish oil.

(6) Four Obesity/Nutrition Research Centers, which concentrate on the study of the natural history of obesity, energy metabolism and diabetes, education and training programs for health care professionals, the impact of neuropeptides on behavior, eating disorders, and epidemiology, behavior modification and relapse in the treatment and prevention of obesity.

(7) Twelve George M. O'Brien Kidney and Urological Research Centers, which support interdisciplinary basic, clinical, and applied aspects of research in renal physiology and pathophysiology, nephrology, and urology. The goal of these centers is to reduce the incidence of mortality and morbidity from kidney and urologic diseases such as end-stage renal disease, kidney disease of diabetes mellitus, and benign prostatic hyperplasia.

(8) Two Research Centers of Excellence in Pediatric Nephrology and Urology, which support research on the basic cellular and molecular pathogenesis of pediatric nephrologic and urologic diseases and disorders. The goal of these centers is to foster and extend the development of new approaches into the causes, early diagnoses, improved treatment, and where possible, the prevention of urological and kidney diseases such as polycystic kidney disease, IgA nephropathy, and the hemolytic uremic syndrome in the pediatric population.

(9) Three Centers of Excellence in Molecular Hematology, which are intended to promote the development of the broad range of scientific expertise and technologies needed for the investigation of genetic diseases and genetic therapy and emphasize the study of gene structure and function, the structural biology of proteins, and the

mechanisms of hematopoietic cell maturation and differentiation. The goal of the Centers is the development of preventative, curative, or intervention strategies in the treatment of genetic diseases.

PUBLIC EDUCATION ACTIVITIES

Mr. Porter: How much is included in your 1997 budget for public education activities?

Dr. Gordon: In FY 1997, the NIDDK will spend about \$4.5 million on programs to disseminate information about research results to health professionals, patients and the public. The NIDDK develops and disseminates health-related fact sheets, newsletters, brochures, and posters. The Institute supports media outreach activities in diabetes, and a long-term community-based health campaign, "Sisters Together," a prototype established to raise awareness of the importance of healthful eating and exercise in obesity-prone minority communities. We disseminate information through the National Diabetes Information Clearinghouse, the National Digestive Diseases Information Clearinghouse, the National Kidney and Urologic Diseases Information Clearinghouse, the National Diabetes Outreach Program, and the Weight-control Information Network.

COLLABORATIONS WITH NIH OFFICE OF MINORITY HEALTH

Mr. Bonilla: Dr. Gorden, can you update me on the progress of the collaboration between your Institute and the Office of Research on Minority Health focusing on diabetes research?

Dr. Gorden: The ORMH has been highly supportive of research relating to diabetes in minorities. For three years, the ORMH has been providing ongoing support to a portion of the Diabetes Prevention Program (DPP), our major clinical trial on prevention of non-insulin-dependent diabetes (NIDDM) in persons at risk for the disease. One-half of the study population of this trial will include minority individuals, reflecting the disproportionate impact of NIDDM in minority populations. Gestational diabetes mellitus (GDM) is a risk factor for development of NIDDM. The ORMH funds are supporting recruitment of minority women with a history of GDM as a study population in the trial. The ORMH also has provided funds to enable us to measure visceral fat in the DPP subjects - a crucial measurement for understanding the links between obesity and diabetes.

In addition, the ORMH is continuing its support for a study of the pathogenesis of NIDDM in Mexican American women that should enable us to understand some of the differences in this disease in minorities. The clinical trial of obesity treatment in minority women that ORMH is co-funding may have important implications for diabetes, because obesity is a major risk factor for diabetes. ORMH also has supported a range of projects examining pilot interventions in diabetes in several different minority populations as part of our joint diabetes genes/diabetes treatment initiative.

In FY 1996, the ORMH has agreed to provide funding for two new grants in obesity/diabetes genes in minorities, as well as an ongoing supplement, in order to help sustain the exciting new research that is developing in these areas. Finally, the ORMH has been generous in providing training support and transition funds to minority investigators to help further careers of researchers in diabetes-related areas.

Mr. Bonilla: How is diabetes research supported by ORMH coordinated with NIDDK? In your opinion, are there adequate resources in this area?

Dr. Gorden: I would like to take this opportunity to thank Dr. Ruffin for the tremendous support he has given to the NIDDK and to diabetes research over the past few years. I believe that we have developed a very productive working relationship between our organizations that has led to development of important research that has the potential to improve minority health.

As far as coordination of diabetes research is concerned, each year, Dr. John Ruffin, who is the NIH Associate Director for Research on Minority Health and the Director of the NIH Office on Minority Health, asks for our best ideas for important research opportunities within our mission that relate to minorities. He has been highly receptive to every diabetes concept that we have suggested - all the way from diabetes and obesity genes research, to targeted pilot studies in various minority populations. Once the concepts of mutual interest have been chosen for ORMH funding, the NIDDK is responsible for the day-to-day management of the initiatives, generally as investigator-initiated research grants or as part of a clinical trial. Where appropriate, the ORMH has participated in RFAs with us, for

example, in the development of the Diabetes Prevention Program, our major NIDDM clinical trial. Of course, we provide Dr. Ruffin with a detailed report each year to let him know of the progress of our joint initiatives.

INFLAMMATORY BOWEL DISEASE

Mr. Dickey: Can you briefly explain to me the institute's progress in researching Crohn's disease.

Dr. Gorden: Crohn's disease and ulcerative colitis are extremely complex disorders and are the major cause of morbidity from intestinal illnesses in the United States. The cause of these two diseases remains unknown and, perhaps for that reason, therapies are still unsatisfactory. We believe that advances in medical care for Crohn's disease and ulcerative colitis most likely will arise from better understanding of the cause of these diseases. In the last three to four years, researchers have developed some new and exciting animal models of ulcerative colitis and Crohn's disease that promise to shed some important light on their causes and to provide models to test medications and new approaches to therapy. These models were developed using the powerful techniques of modern molecular biology. The animal models were developed by either giving them a new gene -- so called transgenic animals -- or taking away one of their own genes -- so called "knock out" animals. For instance, there is now a transgenic rat which develops small and large bowel inflammation as well as arthritis and iritis -- inflammation of the iris of the eye-- features that closely resemble Crohn's disease. There is a "knock out" mouse that develops inflammation of the colon that closely resembles ulcerative colitis. A third model has an abnormal T-cell receptor and develops chronic intestinal inflammation without ulcers, while a fourth deletion model develops inflammation of the colon that leads to cancer. It is very likely that the susceptibility to chronic intestinal inflammation found in these models is also present in humans who develop ulcerative colitis or Crohn's disease. These models also show the importance of the environment, in that these animals do not develop chronic inflammation of the colon if they are raised in a germ-free environment -- without bacteria in the intestine -- which occurs normally in all animals and humans. Thus, these models are providing insights into how the normal intestine maintains a balance between the immune system, the intestinal cells and the bacterial environment. Inflammation comes about if there is a disturbance in this balance, and regulating the balance may be the key to management and control of Crohn's disease and ulcerative colitis. Sorting out the background genes and specifically altered genes that lead to intestinal inflammation will help investigators to develop novel immunologic approaches to intestinal disease, such as gene therapy, use of immune cytokines, and correct management of immunologically active medications for these important digestive diseases.

PROSTATE DISEASE

Mr. Stokes: As you know, African American males have the highest rate of prostate cancer than any other segment of the world's population. The "Medical Treatment of Prostate Disease Clinical Trial" has a significant opportunity to address the issue of prostate disease in minorities. Are any specific plans being developed to utilize the trial to address this disease?

Dr. Gorden: The NIDDK-supported "Medical Treatment of Prostate Disease Clinical Trial," co-funded with the NIH Office of Research on Minority Health (ORMH), is comparing the effects of different medications on the prevention of progression of symptoms of benign prostate disease. The benign prostatic hyperplasia (BPH) clinical trial is expected to provide insights about the natural history and effective treatment of various prostate diseases, including chronic prostatitis. The trial is being conducted at 17 centers throughout the United States. Minority recruitment is being encouraged at all centers; however, a number of centers are more actively involved in minority recruitment. They include: Yale University, New Haven, CT; Emory University, Atlanta, GA; Baylor College of Medicine, Houston, TX; Vanderbilt University, Nashville, TN; Columbia Presbyterian Medical Center, New York, NY; University of Texas Southwestern Medical Center, Dallas, TX; Washington University, St. Louis, MO (NIDDK is funding a supplement to this center for an African American urologist to develop specific minority recruitment strategies); and the Henry Ford Hospital, Detroit, MI, funded by the ORMH. To further enhance minority recruitment, the BPH Steering Committee is planning a workshop designed specifically to educate investigators on minority recruitment strategies and plans to invite outside speakers experienced in this area.

Mr. Stokes: What valid data are available on prostate diseases in minorities? Are there any current or planned data collections to address these issues?

Dr. Gorden: The NIDDK is supporting a major clinical trial on benign prostatic hyperplasia (BPH) that is expected to provide insights about the natural history and effective treatment of various prostate diseases. One goal of the trial is to enroll a significant number of minority men with BPH. Through biopsies that are obtained, the Institute hopes to glean information about the entire spectrum of diseases of the prostate, such as their underlying processes and their progression. We hope that the data will provide valuable information on possible racial differences in the incidence of prostate disease and on the clinical course of the disease. Additionally, the NIDDK has discussed with the American Urological Association the possibility of compiling a compendium of data for urological diseases generally. This compendium may be modeled after the NIDDK publications "Diabetes in America" and "Digestive Diseases in the United States: Epidemiology and Impact."

GENE REPOSITORY

Mr. Stokes: What can you tell us about the status of the gene repository as it relates to these diseases?

Dr. Gorden: The NIDDK does not sponsor research on a gene repository. The Institute does, however, lead the Federal research effort on urological diseases, including prostate disorders. As you may know, our urology program began as a small component of the NIDDK and has grown about 300 percent over the last five

or six years, fueled largely by initiatives that are related to prostate disease. These initiatives have related to both benign prostate disease and to prostate cancer, an area in which we collaborate with the National Cancer Institute (NCI). Program growth has been largely related to both Congressional directives and Institute initiatives to address what are considered major health problems within the purview of urology.

The aim of the NIDDK prostate research program is to promote and fund basic and clinical research which will further the understanding of the basic science of prostate growth regulation, the foundation for research into prostate diseases. The NIDDK accomplishes this using a number of different mechanisms, which are described below.

There are a total of five George M. O'Brien Urologic Research Centers, with four having an emphasis on prostate disease, three of which are co-funded by the NCI through an Inter-Institute Working Agreement. The Center at the Sloan-Kettering Institute for Cancer Research conducts studies to identify and characterize tumor cell surface antigens and isoenzymes associated with tumor progression. These studies involve the use of human prostate tissue as well as tissue from animal models. Studies at the Southwestern Medical Center focus on the regulation of benign and malignant prostate cell function(s) involving androgen receptor and 5-alpha reductase expression in benign prostatic hyperplasia (BPH). Studies conducted at the University of Washington involve the development of animal models of human prostate cancer. Studies conducted at these three centers are co-funded by the NCI. Studies conducted at the Northwestern University Medical School, which are funded solely by the NIDDK, include the biochemical analysis of the human prostate; the cultivation and characterization of epithelial and mesenchymal components from neonatal, normal, and hyperplastic human prostate tissues; and the refinement of an acceptable model for the study of BPH.

Also relevant is the NIDDK-supported clinical trial on BPH, co-funded with the Office of Research on Minority Health (ORMH), comparing the effects of different medications on the prevention of progression of symptoms of benign prostate disease. The BPH clinical trial is expected to provide insights about the natural history and effective treatment of various prostate diseases, including chronic prostatitis. Through biopsies obtained in this trial, the NIDDK hopes to gain knowledge about the entire spectrum of diseases of the prostate, such as their underlying processes and their progression. For example, these biopsies will show the percentage of men with infected or inflamed prostate tissue, information that will enable investigators to relate these clinical parameters to change in symptoms. In testing drugs to treat BPH, we hope to learn how best to reduce symptoms such as urinary frequency and discomfort that are related to more than one prostate disease.

The NIDDK also funds a number of individual research projects that focus on basic and clinical aspects of normal and abnormal prostate growth and function. Many of these projects are conducted by investigators drawn from other disciplines into prostate research.

Mr. Stokes: What is the status of the gene repository as it relates to African Americans, and other minorities?

Dr. Gorden: The NIDDK does not support research on a gene repository. We understand, however, that the National Center for Human Genome Research

(NCHGR) at the NIH has awarded an institution classified as a "Historically Black College and University" a planning grant to develop a reference resource using DNA samples from African American families, complimentary to a similar source of DNA for Caucasians. We also understand from the NCHGR that this reference resource has been used internationally to develop a genetic map of the human genome and to help isolate specific genes causing or contributing to various common and genetic diseases. The NIDDK has been informed that the application to actually develop the resource has not yet been submitted to the NIH for consideration.

CLINICAL TRIALS

Mr. Stokes: What are some of your other most significant clinical trials, specifically what can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Gorden: Patient recruitment for the Hemodialysis (HEMO) Clinical Trial, which is designed to determine whether a higher than usual dose of dialysis and high-flux dialyzers can significantly improve morbidity and mortality in hemodialysis patients, began in April 1995 at 15 medical centers located throughout the United States. Recruitment is currently on target; 300 of the 900 expected study participants have been enrolled into the trial. When the study was formulated, it became apparent that there was a need for more standardized approaches to many dialysis procedures. Therefore, it was necessary to define specific parameters, many of which will become standards by which dialytic therapy will be provided in the U.S., constituting important advances in the field. Six scientific abstracts on special studies carried out in the clinical trial were presented at this year's annual meeting of the American Society of Nephrology. Two of the abstracts are of particular importance in advancing the field of dialysis.

In FY 1994, the NIDDK released an RFA entitled "Progression of Renal Disease: IgA Nephropathy in Children and Young Adults." The Baylor Research Foundation was awarded money to conduct a multicenter clinical trial examining the role of prednisolone for the treatment of IgA nephropathy in children and young adults. A third arm of this study has recently been approved that allows for the study of omega-3 fatty acid on renal function.

The African American Study of Kidney Disease and Hypertension (AASK) is a clinical trial designed to evaluate whether lower than usual blood pressure control alone, or in combination with certain classes of antihypertensive drugs, can slow the progression of hypertension-related kidney disease in African Americans. The full-scale phase of the AASK began July 1, 1994. Randomization of patients into the trial began in the Spring of 1995. All clinical centers are actively recruiting new patients for participation in the study. Previous clinical trials of chronic renal disease have not enrolled participants with the demographic and clinical characteristics observed to date in participants randomized in the AASK Trial. These unique demographic and clinical characteristics offer significant challenges in recruitment and retention of participants. The NIDDK hopes that several regional colloquia and local news briefs will help solve these recruitment problems.

Our newest clinical trial for diabetes, called the Diabetes Prevention Program, or DPP, is designed to actually prevent or delay the onset of non-insulin-dependent diabetes mellitus (NIDDM) in at-risk populations. Because NIDDM disproportionately affects minority populations, approximately 50 percent of those

enrolled in the DPP will be from those populations. Patient screening and recruitment are scheduled to begin this month. Four thousand patients at high risk for developing diabetes (e.g., obesity or history of gestational diabetes) ultimately will be enrolled at 25 sites in the U.S. These patients will have been determined to have impaired glucose tolerance (IGT), which is a major risk factor for development of NIDDM. IGT is a less severe stage of altered blood glucose control that often precedes Type II diabetes. These 4,000 patients will be randomized into four treatment groups. One of the groups will be given the drug metformin, a second group will be given the drug troglitazone, a third group will receive an intensive diet and exercise intervention, and a fourth will receive healthful lifestyle information about how to prevent diabetes. All of these interventions are aimed at preventing or delaying the progression from the pre-diabetic, IGT state to diabetes, over a period of about 4 and one-half years. All patients will be counseled on healthful diet and exercise habits, and all will be followed closely for their blood pressure, blood lipids, and diabetes status. We are hopeful that at the conclusion of this trial, in about seven years, we will have definitive evidence on how to prevent NIDDM. Evidence of this kind would have major positive human and economic consequences.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Gorden: The NIDDK anticipates a funding level of approximately \$63.1 million for clinical trials in FY 1997. This compares with funding levels of \$49.95 million for FY 1994, \$58.21 million for FY 1995, and approximately \$60.4 million in FY 1996.

Mr. Stokes: What is the Institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Gorden: For large, multicenter clinical trials initiated by the NIDDK, we take steps to ensure appropriate enrollment of minorities in the trial design. For example, our Diabetes Prevention Program (DPP) clinical trial is designed to oversample the minority populations needed for its study. The target cohort for the DPP is approximately 50 percent minorities (African Americans, Hispanic Americans, Native Americans, and Pacific Island and Asian Americans) and at least 50 percent women. In addition, approximately 20 percent of the target cohort is older Americans age 65 years and older.

Screening and recruitment is included in the DPP's protocol design -- location of the clinical research center must be community-based; and language must be a consideration in the selection of the recruitment and retention of coordinators. The recruitment coordinator, with approval of the program coordinator and the principal investigator, is required to develop a clinic-specific recruitment strategy. Clinics, where appropriate, are urged to form Advisory Boards and hold community meetings to support and assist in formulating the message and methods for publicity and participant recruitment. A variety of methods are used to contact community members including, for example, work-site mailings and publicity, hospital record reviews, mass mailings, and public service announcements. An annual progress report is required from the study to assure compliance with the protocol, and to assess recruitment and retention of minority subjects.

The NIDDK also includes the complete narrative of NIH policy on special instructions to applicants regarding implementation of NIH policy concerning inclusion of women and minorities in clinical research study populations in its guidelines that applicants are required to follow in responding to solicitations for clinical trials.

MINORITY INVESTIGATORS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your institute?

Dr. Gorden: I can tell you that the NIDDK continues to seek new ways to stimulate greater research interest from minority investigators. In February, 1996, the NIDDK issued an RFA entitled "Support of Minorities in Diabetes, Digestive, and Kidney Disease." This mechanism (R03-small research grant) provides an opportunity for minority researchers to accept a tenure-earning position, gain additional research experience, and obtain preliminary data on which to base a subsequent research grant application in the areas of diabetes, endocrinology, metabolism, digestive diseases and nutrition, kidney, urology or hematology. New awards hopefully will be made in FY 1997.

KIDNEY DISEASE AND HYPERTENSION

Mr. Stokes: African Americans with hypertension are much more likely to develop end-stage renal disease than the general population. What major research activities are underway at the Institute to address this problem?

Dr. Gorden: End-stage renal disease (ESRD) associated with hypertension is a major health problem among African Americans. A number of factors have been proposed to be responsible for this increased disease burden in African Americans, including greater prevalence of hypertension, more severe and uncontrolled hypertension, and greater susceptibility of the kidney to the effects of high blood pressure. The African American Study of Kidney Disease (AASK) is a clinical trial designed to evaluate whether lower than usual blood pressure control alone, or in combination with certain classes of antihypertensive drugs, can slow the progression of hypertension-related kidney disease in African Americans. The pilot phase of the AASK, which tested the feasibility of conducting a large trial, began in July of 1992 and was completed in June of 1994. The full-scale phase of the AASK began July 1, 1994. Randomization of patients into the trial began in the Spring of 1995. The expected completion date of the study is the year 2000, with results expected to be available in the year 2001.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum. What are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Gorden: Within the past year, the NIDDK began two new programs to accelerate the public's knowledge and understanding of health messages for diabetes

and for prevention of obesity. The National Diabetes Outreach Program disseminates the results of the 10-year NIDDK Diabetes Control and Complications Trial to the public through the "Do Your Level Best" campaign, which emphasizes control of blood glucose levels in order to prevent complications of diabetes such as blindness, amputations, and kidney disease. The outreach program's "Feet Can Last a Lifetime" campaign promotes simple techniques of footcare to health professionals and the public through the news media and through a partnership of federal and private sector organizations.

Another new program, the Weight-control Information Network (WIN), promotes increased exercise and good nutrition through a pilot program for African American females between the ages of 18 and 35 in three communities in Boston, Massachusetts. The campaign, called "Sisters Together: Move More, Eat Better," involves a consortium of the New England Medical Center, Tufts University, and the Harvard School of Public Health. The WIN also develops fact sheets and other materials to translate the results of research and the position papers of the National Task Force for the Prevention and Treatment of Obesity.

The total funding level for these outreach and public education programs during FY 1994 was \$.6 million; in FY 1995, \$.3 million; in FY 1996, \$1.3 million; and in FY 1997, \$1.4 million.

In addition, the NIDDK has over 20 years of experience in dissemination of information through the National Diabetes Information Clearinghouse, the National Digestive Diseases Information Clearinghouse, and the National Kidney and Urologic Diseases Information Clearinghouse. By targeting health professionals as the link to the public, the national clearinghouses play a major role in getting the results of research to the audiences most likely to use and communicate these results. The total funding level for the clearinghouses during FY 1994 was \$2.11 million; in FY 1995, \$2.14 million; in FY 1996, \$2.15 million; and in FY 1997, \$2.2 million.

There are also salaries, printing costs and other costs of conducting activities to inform the public, within the research management and support portion of the budget. These costs, together with the above costs of the outreach and public education programs and the clearinghouses, yield the following grand totals: in FY 1994, \$3.6 million; in FY 1995, \$3.6 million; in FY 1996, \$4.3 million; in FY 1997, \$4.4 million.

Mr. Stokes: In most of the institutes, these programs are funded in the research management and support account. Is this the case in your Institute? If so, have you been able to maintain these programs in spite of the funding reduction in the budget account? In which outreach areas are you hurting the most?

Dr. Gorden: The largest part of the cost of the NIDDK's public education and outreach programs are in the contracts mechanism rather than the research management and support mechanism. In order to support these programs, and in particular to begin the recently-initiated National Diabetes Outreach Program and the Weight-control Information Network, we have ended some older research resource contracts. However, the FY 1996 cuts in research management and support resulted in a 50 percent reduction in the printing of new and revised health information pamphlets for patients and physicians, and campaign materials for the outreach program. These cuts will have an adverse affect in providing the latest and best information for several of the diseases under NIDDK purview.

NIDDK COLLABORATIONS WITH THE NIH OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: What collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Gorden: Over the past three years, the NIDDK and the NIH Office of Research on Minority Health (ORMH) have sustained a very productive working relationship. This collaboration has enabled us to jointly promote research on diseases such as diabetes, obesity, and kidney diseases that disproportionately affect minority populations. Most of our efforts with ORMH involve co-funding of specific projects, however, in the case of one major initiative, we developed an arrangement in which we alternate years of support. Beginning in FY 1994, the ORMH and the NIDDK undertook a joint initiative to address both basic research on the genetic aspects of diabetes in minority populations and new approaches to treatment and prevention of diabetes in these groups. This initiative reflected the outcome of an RFA developed by the NIDDK to encourage research in minority populations, as well as a Congressional directive relating to the genetics of diabetes in minorities. The collaboration was formalized in a memorandum of agreement that described a three year effort, with ORMH and NIDDK each contributing \$2,000,000 per year to the joint efforts. I would like to emphasize that an overall initiative of this magnitude could not have been undertaken without ORMH support. In FY 1994, the first year of the collaboration, ORMH funds were used to pay a number of grants relating to genetics of diabetes in minorities, while the NIDDK paid for several grants investigating treatment of diabetes in a range of minority populations. In FY 1995, the support was reversed, with ORMH funding the treatment grants (listed below), and NIDDK supporting the genetics research. Thus, from an accounting standpoint, the ORMH provided the total support for the following grants in FY 1995, as part of the 3-year overall collaborative initiative with the NIDDK:

1. Enhanced Diabetes Care for African-American Children (\$241,565).
2. Improving Primary Care of African Americans with NIDDM (\$78,093).
3. Trial of Prevention in African Americans with NIDDM (\$142,684).
4. Improving Metabolic Fitness in Obese Adolescents (\$237,751).
5. Antidiabetic Drug Intervention in African Americans (\$223,323).
6. Prevention of NIDDM in Centrally Obese African Americans (\$250,589).
7. Diet Change in NIDDM Caribbean Latinos (\$312,498).
8. Dietary Changes in African American Women by Activation (\$264,357).
9. Education and Group Support for Diabetic Hispanics (249,139).

For FY 1996, we have been informed that ORMH expects to sustain and enhance its joint efforts with the NIDDK, which include the initiative described above and a number of additional co-funded studies.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Gorden: There are specific projects, totaling \$31,752,245, that are co-funded by the Institute (\$25,867,463 or 81.5 percent), and the ORMH (\$5,884,782 or 18.5 percent), which considerably enhance our ability to fund studies in diabetes, bionutrition, obesity, and training for minority investigators, and which we would not have been able to sustain without our partnership with the ORMH. In addition, the ORMH and the Institute are working on new collaborations which will serve to strengthen research in minority populations, and we have been informed that ORMH intends to sustain and enhance this commitment for FY 1996.

For the record, we are providing a complete listing of these jointly-funded projects which were funded during FY 1995:

1. Investigation of Human Obesity Genes in Minority Populations (ORMH=\$119,000, and NIDDK=\$1,140,000). The NIDDK contribution represents the ongoing efforts of our Obesity/Nutrition Research Center at Rockefeller University, where the ob gene was discovered and research on obesity genes is proceeding rapidly. The ORMH provided supplemental funds to augment the study of these genes in minority populations.
2. Magnesium and Sickle Cell Disease (ORMH=\$99,020, and NIDDK=\$1,665,852).
3. Benign Prostate Hyperplasia Trial (ORMH=\$225,000, and NIDDK=\$299,698).
4. Assessment of Visceral Adiposity in Diabetes Prevention Program (ORMH=\$800,000, and NIDDK=\$18,599,000). The NIDDK contribution represents the overall funding for the Diabetes Prevention Program (DPP), which will be enrolling over 50 percent minorities. The ORMH contributed funds to allow an additional measurement, which will assess visceral adiposity, to be performed on DPP participants.
5. Training and Career Development of Minority Investigators and Transitional awards (ORMH=\$840,141, and NIDDK=\$650,000).
6. Gestational Diabetes Component of DPP Clinical Trial (ORMH=499,999; [Note: NIDDK=\$18,599,000 counted with #4 above], and other Organizations=\$500,000). As in #4 above, the ORMH contribution enabled the addition of a component to the DPP trial, which is enrolling over 50 percent minorities.
7. Pathogenesis of NIDDM in Mexican American Women (ORMH=\$195,450, and NIDDK=\$235,432).
8. Long-term Outcome of Obesity Treatment in Minority Women (ORMH=\$304,184, and NIDDK=\$235,432).
9. Funding for Minority-Majority Collaboration in Conjunction with African American Study of Kidney Disease and Hypertension (AASK) and Support for AASK Clinical Center at Howard University (ORMH=\$742,351, and NIDDK=\$742,351).
10. Diabetes Genes, Treatment and Prevention in Minorities Research Initiative (ORMH=\$2,000,000, and NIDDK=\$2,000,000).
11. Heredity Hemolytic Anemia Outreach Clinics (ORMH=\$59,634, and NIDDK=\$299,698).

GENE THERAPY

Mr. Stokes: How critical is gene therapy research to furthering advances in areas of research which are under the purview of your institute? What diseases and disorders would benefit from enhanced research in this area?

Dr. Gorden: Research programs supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in the areas of molecular genetics and cell biology have helped to form the knowledge base for current human gene therapy protocols. In ongoing studies, NIDDK-supported researchers are identifying genetic defects involved in diabetes and in endocrine, metabolic, digestive, kidney, urologic, and hematologic diseases. They are also developing animal models for gene therapy, techniques for gene targeting, methods for gene transfer (vectors), and methods of controlling gene expression. Inborn errors of metabolism, such as cystic fibrosis, is a particular focus for NIDDK-supported gene therapy research. NIDDK-supported research on the hemoglobin molecule, which has provided important information about gene expression, continues to make major contributions to this field.

Diseases and disorders that might benefit from enhanced gene therapy research include: hematologic diseases such as sickle cell anemia, Cooley's anemia, hemophilia, and iron storage and transport diseases; kidney and urologic diseases such as polycystic kidney disease, kidney disease of diabetes mellitus, IgA nephropathy, Goodpasture's Syndrome, urinary stone disease, and cystinuria; liver diseases such as familial hypercholesterolemia, Wilson's disease, and Crigler-Najjar syndrome; metabolic diseases such as cystic fibrosis, adenosine deaminase deficiency, and Gaucher disease; and diabetes and other endocrine disorders such as generalized resistance to thyroid hormone, vitamin D resistance, and androgen insensitivity.

KIDNEY TRANSPLANTATION

Mr. Stokes: African Americans have a higher rejection rate for cadaveric kidney transplantation than any other population. Is the institute conducting or supporting research in this area?

Dr. Gorden: Renal transplantation is the preferred therapy for most individuals with end-stage renal disease (ESRD). Unfortunately, the rate of organ donation by many minorities has been very low. The NIH Office of Research on Minority Health has awarded a five year educational grant, referred to as National Minority Organ Tissue Transplant Education Program (MOTTEP), to promote minority donor awareness and to improve the donation process in minority communities. MOTTEP offices are currently being set up in minority communities in 15 states. The NIDDK will be providing administrative support for grant management. The establishment of the MOTTEP program constitutes a major step in solving an important problem in the area of renal transplantation.

ORGAN DONATION

Mr. Stokes: I understand that 27 percent of whites as compared to 11.5 percent of African Americans are willing to donate their organs after death. In addition, 76 percent of the population is aware of organ donor cards, and 18 percent have signed one. While 65 percent of African Americans are aware of donor cards, only 5 percent have signed one. Doctor, what should we be doing to increase outreach to minorities in an effort to improve this situation?

Dr. Gorden: It has been suggested that a major reason minorities are not donating organs may be the lack of appropriate information. Therefore, the NIH ORMH awarded Howard University a 5-year educational grant, referred to as National Minority Organ Tissue Transplant Education Program (MOTTEP), to

improve the organ donation process in minority communities through the use of public education. MOTTEP offices are currently being set up in minority communities in 15 states: Birmingham, AL; Los Angeles, CA; Washington, DC; Atlanta, GA; Honolulu, HI; Chicago, IL; Brooklyn, NY; Albuquerque, NM; Cleveland, OH; Nashville, TN; Detroit, MI; Richmond, VA; Miami, FL, Anchorage, AK; and Houston, TX. The NIDDK will be providing administrative support for grant management.

MINORITY HIGH SCHOOL STUDENTS PROGRAM

Mr. Stokes: I understand that the Institute supports a minority health high school student summer biomedical research program. What is the purpose of the program and how long has it been in existence? What mechanism has been put in place to ensure its continuation?

Dr. Gorden: Since 1990, the NIDDK has taken a lead position in bringing minority high school students to the NIH for laboratory research experience. Students are taught hands-on research by NIDDK researchers in their science laboratories. This program continues to establish mentor-intern relationships that foster careers in biomedical science.

In 1995, a collaboration with the ORMH resulted in ORMH support to minority high school students in laboratory settings in 12 States and the District of Columbia. In 1996, to ensure the continued support of this program for summer high school students, the NIDDK's commitment will provide stipend costs for students and mentor expenses. Additional costs for the students to attend a meeting at the conclusion of the program will be covered by the NIH Office of Research on Minority Health.

H. PYLORI AND PEPTIC ULCER DISEASE

Mr. Hoyer: I understand that the NIDDK has made major progress on a trans-institute initiative with the Office of Research on Minority Health for further research on the relationship between *H. Pylori* and peptic ulcer disease, as well as gastric cancer. I understand that this is being undertaken in collaboration with, and with private funding from, the American Digestive Health Foundation. I would like to congratulate you on the progress you have made in this area and ask that you keep me informed of this very important effort.

Dr. Gorden: I have been pleased to be able to work with Dr. John Ruffin, who is the NIH Associate Director for Research on Minority Health and the Director of the NIH Office on Minority Health, in leading this trans-NIH initiative concept. *H. pylori* infects the gastric mucosa of humans and is present in a large proportion of the world's population. Chronic infection with *H. pylori* can lead to gastric and duodenal ulcer disease, chronic gastritis, and gastric malignancy. Eradication of the organism has been shown to induce long-term remission in peptic ulcer disease, but the pathogenesis of the organism in other gastric conditions and in different populations has not been extensively investigated. *H. pylori* infection rates are higher in African Americans and Mexican Americans, although this may be related to socioeconomic status. Subjects with *H. pylori* infection are three to six times more likely to develop gastric cancer; and gastric cancer is more prevalent in African Americans.

This initiative is our first research collaboration with the American Digestive Health Foundation, which has been actively working with us on the concept. In the past, we also have developed collaborations with the Cystic Fibrosis Foundation and the Juvenile Diabetes Foundation to aid in funding research in those areas. I will certainly keep you informed of our progress on the *H. pylori* initiative.

Mr. Hoyer: I understand that the NIAID will be participating in this effort, and that the NCI and the NICHD have also been invited to join. When do you expect to have your complete team assembled? Will the NCI and the NICHD be joining you? Will you be inviting any other Institutes to participate?

Dr. Gorden: Dr. Ruffin and I initially sent a letter to the Directors of the NIAID, NICHD, and NCI concerning the development of an *H. Pylori* in Minority Populations initiative. Dr. Fauci and Dr. Alexander already have designated representatives to meet with us to discuss the concept further. I understand that the executive committee of the NCI will be reviewing the concept in the near future. In the past, we co-sponsored an RFA with the NCI on the role of helicobacter in cancer, so our staff already has a close working relationship the NCI staff in the *H. pylori* research area. We have not yet held a meeting of all the potential participants, but I know that some preliminary calls have taken place, so I expect that the planning team will meet soon.

Our initial invitation to join in developing an initiative was to the Institutes where we know there are substantial related research interests. Of course, any other Institutes would be welcome to participate. Indeed, in general, the NIH circulates drafts of RFAs internally (on the computer) before they are announced publicly, to maximize the potential for obtaining cosponsors.

INSULIN-DEPENDENT DIABETES

Mr. Hoyer: Over the past few weeks, the *Washington Post* has reported on two studies related to diabetes. One study conducted under the auspices of the National Institute for Dental Research deals with a protein linked to juvenile diabetes and could lead to new methods of diagnosis and treatment. The other study, out of the University of Miami, involved transplantation of pancreas islet cells. Could you comment on these and any other important breakthroughs in the area of diabetes?

Dr. Gorden: Intramural scientists at the National Institute of Dental Research are investigating the molecular biology of diabetes, which is known to increase the risk of gum disease and tooth loss. The researchers identified two marker proteins for insulin-dependent diabetes mellitus (IDDM). The presence of antibodies to these proteins in otherwise normal individuals was highly predictive in identifying those at risk of ultimately developing diabetes. The identification of these proteins will make it possible to develop a new test for screening large populations for IDDM, and may help uncover the actual cause of the disease. I will defer, however, to the National Institute of Dental Research, which supported this research, for a full description of the implications of this study.

The University of Miami study you refer to was an announcement by researchers there of a pilot study they are about to undertake to test, in patients with IDDM, whether bone marrow infusions given with pancreatic islet cells from the same donor can survive long-term without the use of drugs that suppress the immune system to prevent rejection of the cells. The intent of the investigators, who are NIDDK grantees, was to inform potential volunteers about the pilot study and the criteria for participation, and thus, encourage recruitment of patients into the study. This study is one of several approaches the researchers at the University's Diabetes Research Institute are using to find a feasible protocol for treating insulin-dependent diabetics with transplanted insulin-producing cells while sparing the use of immunosuppressive drugs, which have serious long-term side effects. Initially, the trial will be limited to patients with severe form of insulin-dependent diabetes who have poorly controlled diabetes but who have not yet developed significant complications from their disease. If successful, the trial will be expanded to accommodate other diabetic patients.

This past year, NIDDK grantees reported exciting progress in diabetes research, examples of which are described in the FY 1997 Budget Justification. Briefly, researchers have uncovered new information about the interplay between components of the immune system, an individual's genetic makeup, and the environment in the development of IDDM. It appears that under certain genetic conditions, viruses are capable of triggering the development of IDDM. The prevention of IDDM is a major goal of research. In the past few years, investigators have been able to establish immune, metabolic and genetic screening tests to identify individuals at high risk for the development of IDDM. Researchers also have shown, in animal models and in preliminary human trials, that low-dose insulin therapy may prevent or delay the onset of the clinical manifestation of IDDM. Thus, scientists have the tools to identify individuals at high risk of IDDM and to intervene with a safe and, hopefully, effective therapy. These tools are being applied in an NIDDK-sponsored multi-center clinical trial to prevent or delay the onset of IDDM, called the Diabetes Prevention Trial-1.

In research on non-insulin-dependent diabetes mellitus (NIDDM), after nearly 10 years of fundamental research supported by the NIDDK, three important related

advances in receptor and potassium channel biology were reported that will improve understanding of disorders of glucose balance, including diabetes mellitus. These advances have increased understanding of the signals that regulate insulin secretion and identified the cellular target for the sulfonylureas, oral hypoglycemic agents that are widely used in the treatment of NIDDM. These findings reflect the power of molecular medicine to define genetic and metabolic disorders. In another study, the potential of pharmacologic interventions to prevent NIDDM has been evaluated by NIDDK grantees. They showed that the anti-diabetic drug, troglitazone, stimulates insulin sensitivity in liver, muscle, and fat tissue, and reduced the risk of developing NIDDM. Combined with strong evidence that prevention or reduction of obesity lowers the risk for NIDDM, this information forms the basis for a new NIDDK clinical trial to prevent NIDDM, called the Diabetes Prevention Program. This is a multi-center trial of intervention strategies to prevent the onset of NIDDM in people with impaired glucose tolerance or gestational diabetes mellitus who are at high risk for developing NIDDM. Since NIDDM disproportionately affects minorities, the Institute is recruiting minority patients, who will comprise approximately 50 percent of the trial's enrollment. Lifestyle and pharmacologic interventions will be included in this study. Successful efforts to prevent or delay the onset of NIDDM, and thus its toll on health, would have major health and economic consequences.

RESEARCH PRIORITIES, DIABETES FUNDING

Mr. Hoyer: What are your current high priority areas for research at the NIDDK? I have been told by many advocates that levels of funding for diabetes research has been nearly stagnant for the past four years, while overall NIH funding has increased each year. In your opinion, is diabetes an area which deserves a higher proportion of NIDDK funding in the near future? How much research is currently being done in other Institutes which has direct implications for progress in the area of diabetes?

Dr. Gordon: The Institute's priority areas are the major research programs for which we bear statutory responsibility, including diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within these areas, we focus on specific initiatives each year. For example, the NIDDK has initiated several new areas of research, and expanded several other areas, in FY 1996. They include: (1) Complex genome research in non-insulin-dependent diabetes mellitus; (2) Basic science of gene therapy; (3) Bionutrition and obesity research; and (4) Fundamental studies in molecular medicine and cell biology.

The total of all diabetes research support at the NIH was \$261 million in 1991 and by 1995, four years later, that total increased to \$295 million. The increase represents a growth of 13 percent, while the entire NIH budget grew by 23 percent, before the three ADAMHA institutes were added over that time period to the budget.

Within the NIDDK, we have worked hard to maintain diabetes research at very nearly the same proportion of the total in 1995 as in 1991, in the face of a number of demands to increase other research programs. We have also aggressively managed our research portfolio, by replacing some contracted efforts with investigator-initiated research project grants, by favoring individual physician scientist awards and individual research career awards over the larger institutional awards, and initiating exciting new clinical trials and a ground-breaking diabetes outreach program. Of course, there are considerable scientific opportunities available in research applications which we are currently unable to fund. In FY 1996, for example, we estimate that we will fund one in 4 of diabetes research grant applications.

Many NIH institutes, centers, and offices are contributing significantly to investigations of diabetes and its complications, and the NIDDK is collaborating with several of them in these efforts. For example, the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis and Musculoskeletal Diseases, the National Institute of Child Health and Human Development (NICHD), and the NIH Office of Research on Women's Health are participating in the NIDDK's clinical trial for the prevention of insulin-dependent diabetes. The NICHD and the NIH Office of Research on Minority Health (ORMH) are participating in our clinical trial for the prevention of non-insulin-dependent diabetes. The ORMH also is very supportive of several other aspects of our Institute's diabetes research program. Studies of organ-specific complications of diabetes, such as cardiovascular, eye, nervous system, and dental, are being supported by the appropriate institutes.

INSULIN-DEPENDENT DIABETES

Ms. Pelosi: To follow up on my question to you at the hearing on April 23, there was a report in the press last month of a "possible cure" for diabetes involving "a combination of pancreas islet cells and bone marrow transplantation." The news article, which appeared in the March 14, 1996, Washington Post, reported "that an experimental treatment of diabetes has reversed the course of the disease in some patients, allowing them to live without insulin." This research was conducted by Dr. Camillo Ricordi at the University of Miami School of Medicine. Could you provide an assessment of the importance of this research for the discovery of a cure for diabetes?

Dr. Gorden: This study of pancreatic islet transplantation as a treatment for insulin-dependent diabetes is examining whether bone marrow infusions given with islet cells from the same donor can survive long term, without the use of drugs that suppress the immune system to prevent rejection. If successful, this trial may lead to an advanced therapeutic alternative to daily insulin injections for diabetes.

I would like to discuss one other thing about the reports of this study. The University of Miami study you describe is an example of one of the generic problems we face in communicating accurate information about biomedical research to patients and reporters anxious for a cure. Media reports often misleadingly describe preliminary, experimental research as a new treatment or cure. When this happens, the hopes and expectations of affected patients are falsely elevated, only to be dashed when they seek the purported treatment or cure from health care providers. The story you refer to was developed by Reuter, and appeared in the Washington Post on March 14, 1996, and was subsequently broadcast by other news organizations. This article talks about a "possible cure" for diabetes involving a combination of pancreatic islet cell and bone marrow transplantation. The article focuses on "treatment," and implies that the new therapy has already been tested and is available. It mentions only in the final two paragraphs that the University of Miami is about to begin a pilot study. The approach taken in the article is quite different from that reflected in the news release developed by the University, which makes clear that the real "news" is the inception of the pilot study in which the new therapy will be tested. The NIDDK and the University received several calls following the Reuter story. We did all we could to correct the impression created by the misplaced emphasis on a "possible cure" in the Reuter story, and explained the experimental status of the research. Institute staff also discussed the problem with our grantees at the University, who indicated that they were greatly disturbed by the misleading media coverage. The University's intent in developing the news release and in having a press conference was to inform potential volunteers about the pilot study and the criteria for participation, and thus, to encourage recruitment of patients into the study. Unfortunately, this is just one example of the types of problems we have when media coverage recasts, over-simplifies, or mistakenly reports on biomedical research studies and findings.

DIABETES AND CARDIOVASCULAR DISEASE IN WOMEN

Ms. Lowey: Please provide an update on the collaboration between NIDDK and the Office of Research on Women's Health focusing on cardiovascular disease in women with diabetes. Are future projects planned in this area?

Dr. Gorden: I am very pleased with the collaborative efforts that are developing between the NIDDK and the NIH Office of Research on Women's Health (ORWH). ORWH has provided support for a study focusing on cardiovascular disease among women with insulin-dependent diabetes mellitus (IDDM). This project builds on the results of the Institute's successful Diabetes Control and Complications Trial (DCCT). A major objective of the study, entitled "Epidemiology of Diabetes Interventions and Complications" (EDIC), will be to determine whether the very careful control of blood glucose levels achieved during the DCCT continues to be beneficial, including the effects of such control on cardiovascular disease. The DCCT itself involved 1,400 subjects, approximately half of whom were women, followed for an average of nine years. The trial demonstrated that maintaining blood glucose levels as close to normal as possible can prevent or delay the progression of some of the most serious complications of IDDM as it affects the eye, kidney, and peripheral nerves. The EDIC will examine the effects and interactions of risk factors for cardiovascular disease, as well as the occurrence of cardiovascular events, such as myocardial infarction, coronary artery disease, peripheral vascular disease, angina pectoris, and cardiac arrhythmias. The EDIC also will continue to monitor the effects of the DCCT interventions on development of nephropathy and retinopathy. During FY 1995, the funds provided by ORWH enabled EDIC researchers to conduct carotid ultrasound tests on virtually all of the patients with diabetes in the cohort, including approximately 700 women. In addition, they were able to carry out normative studies on 100 non-diabetic men and women. This collection of normal data will be of general utility to investigators in cardiovascular disease research outside the EDIC. A manuscript is in preparation that describes information obtained thus far. While no significant treatment effects are discernable from the studies performed last year, a number of opportunities are scheduled for examining cardiovascular disease risk factors over the 10-year duration of EDIC, including a repeat carotid ultrasound that is scheduled for year four.

We are working closely with the ORWH to develop future collaborations in the area of diabetes. The ORWH already has committed funds to the Institute for FY 1996 to support an ancillary study to Institute's Diabetes Prevention Program clinical trial that would investigate the abnormal physiology of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in women with and without a previous history of gestational diabetes mellitus (GDM). The ORWH also has indicated its interest in looking at other possible approaches to prevention and treatment of diabetes and its complications in women.

DIABETES RESEARCH OPPORTUNITIES

Ms. Lowey: In testimony before the subcommittee in February, the National Diabetes Research Coalition presented an action plan for curing diabetes. Their testimony reported significant research developments, including islet transplantation, which appear to hold great potential for curing diabetes but require a significant investment of funding. If Congress were to appropriate the \$315 million for

diabetes research that the plan calls for, specifically \$155 million at the NIDDK and \$160 million at other NIH Institutes, could this money be spent wisely?

Dr. Gorden: As you know, Ms. Lowey, it's been the case for many years that there are many more scientific opportunities in diabetes and other fields of research than we are able to support with available funds. This has been true not just for the NIDDK but for the NIH generally. Additional funds would enable the NIDDK to fund a greater number of investigator-initiated grants, and also would enable us to pursue initiatives to encourage research more rapidly and more fully in areas of particularly compelling scientific opportunity.

JUSTIFICATION OF THE BUDGET ESTIMATES

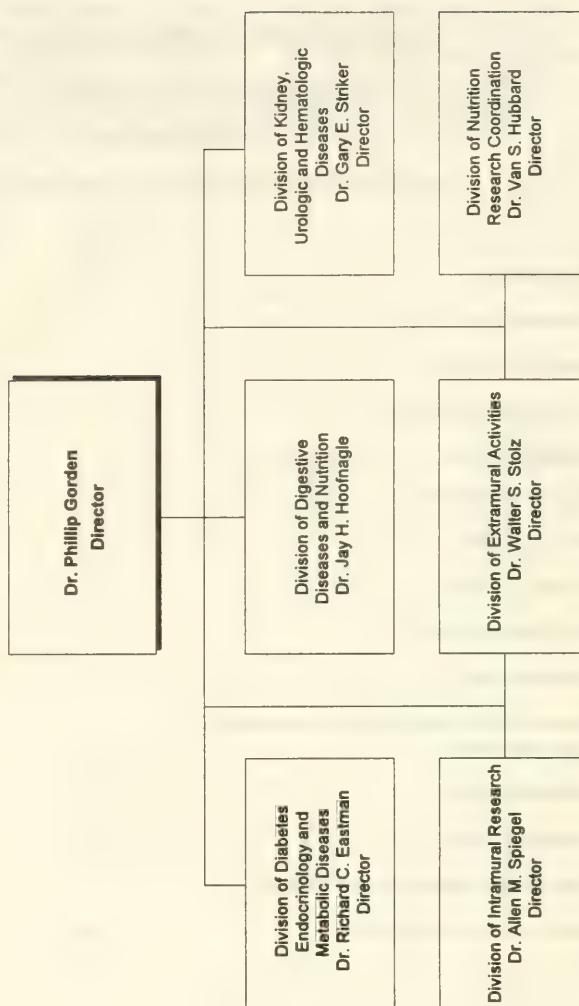
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

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NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, \$772,975,000.

Note—A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$728,284,000	\$771,252,000	\$772,975,000
Reduction in accordance with P.L. 103-333.....	(656,000)		
Rescission in accordance with P.L. 104-19.....	(679,000)		
Subtotal, Adjusted Appropriation.....	726,949,000	771,252,000	772,975,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	(621,000)		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....		(11,735,000)	
Comparative transfer from: Other NIH Institutes for Management Fund adjustment.....	(1,800,000)		
Comparative transfer to/from: Office of the Director, NIH to NIDDK for the Division of Nutrition Research Coordination.....	446,000		
Subtotal, adjusted budget authority.....	724,974,000	759,517,000	772,975,000
Unobligated balance, lapsing.....	(23,000)		
Total obligations.....	724,951,000	759,517,000	772,975,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1995—\$14,498,000; FY 1996—\$14,500,000; FY 1997—\$14,700,000.

Also excludes funding for HIV activities: FY 1995—\$10,752,000; FY 1997—\$11,948,000
included in the Office of AIDS Research, NIH.

Note: Excludes \$145,000 in FY 1995 and \$94,000 in FY 1996 for royalties.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
572	\$724,974,000	590	\$759,517,000	590	\$772,975,000	—	+\$13,458,000

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute of Diabetes and Digestive and Kidney Diseases. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

General Statement

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research related to many serious and costly diseases affecting the public health. These include but are not limited to: diabetes mellitus; endocrine diseases; osteoporosis; metabolic diseases including cystic fibrosis; digestive diseases including those of the liver and biliary tract, pancreas, and gastrointestinal tract; nutrition and eating disorders including obesity; kidney failure; genitourinary diseases; and diseases of the blood-forming organs. Several of these diseases are among the leading causes of disability and death; all seriously affect the quality of life of those who have them; and, each year, their economic burden exceeds \$300 billion.

The Institute places a strong emphasis on basic research in the belief that answers to fundamental biological questions form the basis for improvements in medical care. Institute-supported basic research has led not only to reduced human suffering but also to reduced health costs. Medical treatments for urinary tract stone disease and benign prostatic hyperplasia, for example, have reduced the need for hospitalization and surgery among many patients. Recently, it was estimated that medical treatment of *Helicobacter pylori* infection to prevent ulcer recurrence can save \$400-\$800 million annually in health care costs in the United States. In addition, after many years of basic research on the role of the amino acid glutamine and observations that glutamine levels decline during severe illness or injury, a bone marrow transplantation study this year has shown the economic benefit of glutamine supplements. It showed that, if patients were given supplements of glutamine during recovery from transplantation, a seven-day decrease in hospital stay and a per-patient saving of more than \$10,000 could be achieved. It is likely that other treatments currently being studied experimentally by Institute grantees, such as those to prevent bone loss or those to prevent the complications of sickle cell disease, will also lead to reduced hospital stays and increased health care savings.

Obesity is one of the diseases within the NIDDK mission that most affects the public health. New statistics indicate that over one-third of Americans are sufficiently obese to suffer greater than average risk for developing chronic diseases such as diabetes mellitus, cardiovascular disease, hypertension, gallbladder disease, and certain forms of cancer. It is estimated that over \$50 billion are spent annually on obesity-related illnesses and treatments. Because data suggest that as much as 80 percent of the susceptibility to obesity is due to genetic factors, the Institute has placed an emphasis on the need for research to identify the genes that affect body weight. Last year, NIDDK grantees made a breakthrough discovery: they identified an obesity gene in mice and found a similar gene in humans. The cloning of this obesity gene and the identification this year of its protein product, leptin, have opened up new and exciting avenues for research into the molecular basis of weight control. Studies with leptin in mice have already increased understanding of some of the physiological mechanisms that regulate body weight. Recently, the receptor for leptin in mice and rats has been identified, and appears to be identical with a gene that is associated with gross obesity and diabetes in rodents.

A direct genetic link between obesity and diabetes was revealed, with evidence that the genetic abnormality causing diabetes in mice is likely to be a mutation in the gene for the protein that serves as the leptin receptor. In addition, a recently discovered mutation in another gene, the β_3 -adrenergic receptor gene, links diabetes and obesity in humans. Mutations of that gene were implicated in obesity, weight gain, insulin resistance and/or accelerated onset of non-insulin-dependent diabetes mellitus (NIDDM) in a number of populations, including Caucasians, Mexican Americans, and Pima Indians. The increased research activity building upon the recent discoveries about the molecular underpinnings of obesity engenders optimism that, in the foreseeable future, novel therapies for obesity may be developed and, through obesity prevention, the prevalence of many other common chronic diseases may be reduced. These discoveries relating to the genes for obesity are part of an ongoing NIDDK initiative that focuses on obesity as a total disease entity and a national public health problem.

In addition to genetics, many areas of basic research traverse NIDDK programs, including hormone-receptor interaction, structural biology, development of animal models, and gene therapy technology. This year, investigators have identified a receptor involved in the action of the drugs that have been used to control diabetes. Other studies have focused on receptor pathways involved in the development of hormone-dependent cancers. NIDDK supported research has led to major advances in understanding the biologic roles of parathyroid hormone, its related peptide, and their common receptor, all of which has important implications for the prevention and treatment of osteoporosis. Delta opioid receptors are being explored as candidate targets for new drugs to mediate cocaine-seeking behavior, and an agent with high affinity for sigma receptors is being studied as a promising imaging agent for cancer detection. NIDDK grantees uncovered a new hormone, called urocortin, which may be involved in a number of disorders that result in significant morbidity, such as depression, alcoholism, anorexia, and arthritis. NIDDK structural biologists have determined the solution structure of a complex of the DNA-binding domain of the human sex-determining region Y protein, with the goal of providing the framework for explaining the effects of clinical mutations at the molecular and atomic levels. They have also determined the structure of a second important domain of HIV integrase, an enzyme that mediates the integration of HIV into its host.

The development of a good animal model is a major breakthrough in biomedical research, enabling investigators to move much more quickly in exploring the causes of disease as well as possible therapies. This year, investigators developed a mouse line that should be useful in the delineation of the roles of the related members of the CRF hormone family; rodent models of intestinal inflammation that closely resemble inflammatory bowel disease in humans; a mouse model of Goodpasture syndrome, a disorder of the immune system that affects the kidneys; a mouse strain that lacks the D₂ dopamine receptor subtype, a receptor thought to be involved in schizophrenia, Parkinson's and Huntington's diseases, and hyperactivity disorders; mice bearing the mutant thyroid hormone receptor associated with generalized thyroid hormone resistance, which show both the attention-deficit hyperactivity disorder and reduced weight typical of the human disease; and a mouse model that lacks insulin receptors, which should help determine how specific actions of insulin are modulated by its receptors.

Basic research has led to progress in identifying people at high risk for disease, as well as to clinical investigations of disease prevention and treatment. Investigators have made progress this year in defining who is most at risk for developing gastric cancer and ulcer. They have determined that people infected with *Helicobacter pylori* in early life are more likely to develop gastric cancer and gastric ulcer, and those with a particular strain of *H. pylori* are at higher risk for developing gastric cancer and duodenal ulcer. Researchers have also found evidence that altered expression of a glucose transporter protein may contribute to abnormal kidney function early in diabetes and may be a target for arresting or delaying the development of diabetes-related kidney failure. Improved treatments were reported for cystic fibrosis, which include the use of ibuprofen to improve lung function, and three methods to improve sputum removal from the lungs. Screening tests to identify individuals at high risk for the development of insulin-dependent diabetes mellitus (IDDM) and preliminary animal and human trials showing that low-dose insulin therapy can prevent or delay the onset of IDDM clinical manifestations are presently being applied in an Institute-sponsored multicenter clinical trial to test the effectiveness of this approach. Recent studies showing that lifestyle or drug interventions in patients with impaired glucose tolerance have also led to a large-scale Institute-supported trial to determine how NIDDM might be prevented or delayed. In addition to the two diabetes prevention trials, the NIDDK supports multicenter clinical trials to identify the most effective means of preventing hypertension-related kidney failure in African Americans; to determine the optimum prescription for hemodialysis; and to test the effectiveness of different drugs in the treatment of benign prostatic hyperplasia. The Institute also is supporting a number of small clinical trials to test whether hormonal therapies can have a growth-promoting effect on bone.

The NIDDK works closely with other NIH components to achieve common goals. For example, the Institute leads a major trans-NIH effort in bionutrition research, including an initiative on nutrient modulation of cell repair and maintenance of cell integrity, supported by nine of the NIH institutes, and a program announcement for research on anorexia in disease and aging, sponsored by six institutes. Because many of the diseases within the NIDDK mission disproportionately affect minority populations or women, the NIDDK maintains a close working relationship with the NIH Office of Research on Minority Health and Office of Research on Women's Health, both of which have provided additional support to several NIDDK programs aimed at promoting research to improve the health of minorities and women.

Funding for the NIDDK during the last five years has been as follows:

	<u>Amount</u>	<u>FTE</u>
FY 1992	\$654,893,000	629
FY 1993	\$674,226,000	623
FY 1994	\$704,092,000	597
FY 1995	\$724,874,000	572
FY 1996	\$759,517,000	590

Purpose and Method of Operation

The major program areas of the Institute foster basic, clinical, and applied and developmental research through investigator-initiated research grants, program project grants, research center grant awards, research career development awards, Small Business Innovation Research awards, research and development contracts, and intramural research. Training for research careers and/or teaching is accomplished through National Research Service Awards. Particular emphasis is placed on encouraging individuals from underrepresented minority populations to pursue careers in biomedical research.

Overall Budget Policy

The FY 1997 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases provides a 1.8 percent increase and totals \$772,975,000, an increase of \$13,458,000 over the FY 1996 level.

In the FY 1997 President's Budget Request, the National Institute of Diabetes and Digestive and Kidney Diseases support for research project grants (RPGs) would increase by 4.4 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. In FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 640 competing RPGs, an increase of 202 competing RPGs over FY 1996, and 2,261 total RPGs, an increase of 95 total RPGs over FY 1996.

The FY 1997 request includes funding for 59 research centers, the same level of funding and awards as in FY 1996. The FY 1997 level will fund 216 research career awards, an increase of 6 awards and \$500,000 over FY 1996 and 30 other research grants, the same number of awards and an increase of \$60,000 as compared to FY 1996. The FY 1997 request will fund 926 research trainees, the same level of awards and a decrease of \$861,000 and 42 R&D contracts, a decrease of 3 awards and \$500,000 as compared to FY 1996.

The FY 1997 requests for Intramural Research and Research Management and Support are net decreases. Funding for the intramural program is \$86,657,000, a decrease of \$134,000 below the FY 1996 level of \$86,791,000. Funding for research management and support is \$23,936,000, a decrease of \$105,000 below the FY 1996 appropriation of \$24,041,000.

Extramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act.

Authorization: Indefinite

Budget Authority:

FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate	Increase or Decrease
\$617,709,000	\$648,685,000	\$662,382,000	\$13,697,000

Funding for the Extramural Program during the last five years has been as follows:

	Amount
FY 1992	\$550,770,000
FY 1993	567,725,000
FY 1994	598,647,000
FY 1995	617,709,000
FY 1996	648,685,000

Rationale for Budget Request

The FY 1997 budget request for the Extramural Program is \$662,382,000, an increase of 2.1 percent over the FY 1996 appropriation of \$648,685,000. The FY 1997 extramural request will provide support for the following activities: Diabetes, Endocrinology, and Metabolic Diseases, \$326,720,000, an increase of \$6,760,000 or 2.1% over the FY 1996 estimate of \$319,960,000; Digestive Diseases and Nutrition, \$155,550, an increase of \$3,208,000 or 2.1% over the FY 1996 estimate; Kidney, Urologic, and Hematologic Diseases, \$180,112,000, an increase of \$3,729,000 or 2.1% over the FY 1996 estimate of \$176,383,000.

Diabetes, Endocrinology, and Metabolic Diseases

The NIDDK's Diabetes, Endocrinology, and Metabolic Diseases program has primary responsibility at the National Institutes of Health for extramural research and research training in endocrinology and metabolism, with special emphasis on diabetes, cystic fibrosis, and other diseases and disorders encompassed by these disciplines.

Diabetes

The NIDDK is the lead agency of the Federal government for research efforts to combat diabetes mellitus and its complications. Diabetes is the sixth leading cause of death from disease in the U.S., afflicting an estimated 16 million people in FY 1995, one-half of whom are

undiagnosed. This figure reflects a 50 percent increase in diabetes since 1983, which is believed due to several factors. More Americans are now in the older age range where non-insulin-dependent diabetes mellitus (NIDDM) rates are higher, and the rates of obesity and physical inactivity, both of which are risk factors for NIDDM, have increased. Diabetes is also the leading cause of new adult blindness, kidney failure, and non-traumatic amputation, and is a major risk factor for increased, stroke, heart attack, and premature death. The annual economic cost to the nation of diabetes is estimated to be \$92 billion. In addition, minority populations, including African-Americans, Hispanic Americans, Native Americans, Hawaiians, and Alaskan Natives, are disproportionately affected by diabetes and by its enormous burden.

The Institute's landmark Diabetes Control and Complications Trial showed that very careful management of blood glucose levels dramatically reduces the risk of microvascular complications, such as eye, kidney, and nerve damage, due to diabetes. These important findings have profound implications for the life-long health and quality of life not only for insulin-dependent diabetics, but also for people with the more common non-insulin-dependent diabetes. Therefore, the NIDDK initiated a National Diabetes Outreach Program (NDOP). The NIDDK, in collaboration with the Centers for Disease Control and Prevention, will coordinate NDOP activities. The Institute's inaugural diabetes outreach effort is the patient information book published in 1995 entitled "Do Your Level Best: Start Controlling Your Blood Sugar Today." Other follow up efforts are underway so that people with diabetes and their health care providers can benefit from the knowledge gained from the DCCT and to enhance public awareness of measures that can reduce the risk of developing diabetes and its complications. In addition, Patients from the DCCT are being monitored to determine the longer term impact of careful blood glucose management on complications from diabetes. The NIH Office of Research on Women's Health has funded an assessment to help evaluate cardiovascular disease status in this patient population.

Insulin-Dependent Diabetes Mellitus (IDDM): IDDM affects an estimated 800,000 Americans with onset usually in childhood or early adulthood. In this disease, the immune system, designed to protect us against foreign agents such as bacteria and viruses, initiates a powerful attack to destroy insulin-producing beta cells of the pancreas. Eventually, for survival, affected individuals require insulin from an external source to regulate blood glucose levels.

NIDDK grantees have uncovered new information about the interplay between components of the immune system, an individual's genetic makeup, and the environment in the development of IDDM. Given a certain genetic background and the appropriate environmental trigger, lymphocytes can react to and destroy beta cells. It appears that this happens because the beta cells contain an enzyme that is structurally similar to a component of Coxsackie virus. In susceptible individuals, the lymphocytes mistakenly recognize the beta cell enzyme as foreign and act to kill the beta cell as if it harbored a viral invader, which initiates a cascade of events leading to IDDM. In another study, examination of two patients who had died within a few weeks after developing their diabetes revealed that pancreatic infections had occurred, and that a "superantigen" from an infectious agent had triggered an overwhelming immune response, one much greater than would otherwise be necessary to subdue the infection. All known superantigens are products of either bacteria or viruses. In this case, the superantigen is

postulated to be the causative agent in IDDM. It is thought, therefore, that under certain genetic conditions environmental agents are capable of triggering the development of IDDM.

The prevention of IDDM is a major goal of research. In the past few years, investigators have been able to establish immune, metabolic and genetic screening tests to identify individuals at high risk for the development of IDDM. Researchers also have shown, in animal models and in preliminary human trials, that low-dose insulin therapy may prevent or delay the onset of the clinical manifestation of IDDM. Thus, scientists have the tools to identify individuals at high risk of IDDM and to intervene with a safe and, hopefully, effective therapy. These tools are being applied in an NIDDK-sponsored multi-center clinical trial to prevent or delay the onset of IDDM, called the Diabetes Prevention Trial-1. Approximately 35,000 nondiabetic relatives of persons with IDDM have been screened for this trial and, of these, 0.6 percent are expected to be found at high risk for IDDM. The study goal is to identify and randomize 340 subjects at high risk, either to low-dose insulin treatment or observation. Patients will be followed for four years to determine whether insulin therapy can reduce the risk of IDDM.

Non-Insulin-Dependent Diabetes Mellitus (NIDDM): NIDDM accounts for about 90 percent of all diabetes. What makes NIDDM so insidious is that it often is diagnosed only after it has begun to damage the heart, blood vessels, kidneys, eyes, teeth, and nerves. In addition, as NIDDM develops it becomes increasingly difficult to treat. Therefore, if NIDDM can be prevented, or even significantly delayed, the health and economic implications will be significant.

After nearly 10 years of fundamental research supported by the NIDDK, three important related advances in receptor and potassium channel biology were reported that will improve understanding of disorders of glucose balance, including diabetes mellitus. In pancreatic beta cells, certain energy-related potassium ion channels are crucial for regulating glucose-induced insulin secretion, and are the target for the sulfonylureas, oral hypoglycemic agents widely used in the treatment of NIDDM. NIDDK grantees now have characterized this molecular target by cloning the sulfonylurea receptor (SUR) from hamster cells, and have proposed a mechanism of action for this class of diabetes drugs. The clinical result of malfunction of the sulfonylurea receptor is reported in a companion publication, where "loss of function" mutations in the *SUR* gene appear to cause unregulated insulin secretion despite severe glucose deficiency in a glucose disorder. Normally, insulin is secreted only in response to increased levels of blood glucose. This finding reinforces the notion that the SUR protein has a central role in the regulation of insulin secretion. The authors propose that the mutations in the *SUR* gene result in inappropriately low ion channel activity and excessive insulin secretion. The knowledge from these two studies led to a third investigation in which the electrical and metabolic membrane components that together regulate potassium ion flow, which in turn regulates insulin secretion, were functionally reconstituted. The reconstituted system is similar to that found in native beta cells, is responsive to inhibiting and activating drugs, and thus provides a means for the molecular characterization of this channel and for understanding its role in disorders of glucose balance, including diabetes mellitus. These three findings reflect the power of molecular medicine to define genetic and metabolic disorders.

Impaired glucose tolerance (IGT), characterized by glucose levels between normal and overtly diabetic, was identified by a World Health Organization Study Group in 1991 as the condition that would be most responsive to intervention in preventing the onset of NIDDM. IGT precedes the onset of diabetes and is the first easily recognizable stage in the disease process; 30 to 40 percent of persons with IGT progress to NIDDM. Several risk factors for the progression from IGT to NIDDM have been identified, including obesity and sedentary lifestyles. NIDDK grantees conducted one of the most dramatic studies of the effect of weight loss on progression from IGT to NIDDM. They studied individuals with clinically severe obesity and IGT. The experimental group included patients who underwent gastric bypass surgery. Over an average of nearly six years, experimental subjects displayed a conversion rate to NIDDM that was reduced by 30-fold from the control group not given surgery. Although not practical for widespread application to patients with more moderate levels of obesity, this study reinforces the principle that weight reduction reduces risk for IGT conversion to NIDDM.

The potential of pharmacologic interventions to prevent progression from IGT to NIDDM has been evaluated by NIDDK grantees. They showed that the anti-diabetic drug, troglitazone, stimulates insulin sensitivity in liver, muscle, and fat tissue. In a small group of obese IGT individuals given a weight-maintaining diet, troglitazone reduced the risk of developing NIDDM assessed by various measures. The results of these small studies support the feasibility of troglitazone therapy to prevent or delay onset of NIDDM.

These and other studies provide the foundation for a large scale clinical trial to prevent NIDDM. This NIDDK-supported study, the Diabetes Prevention Program (DPP), is a multi-center clinical trial of intervention strategies to prevent the onset of NIDDM in people with impaired glucose tolerance or gestational diabetes mellitus who are at high risk for developing NIDDM. Since NIDDM disproportionately affects minorities, the Institute is recruiting minority patients, who will comprise approximately 50 percent of the trial's enrollment. Lifestyle and pharmacologic interventions will be included in this study. The trial is a collaborative effort between the NIDDK and other components of the Public Health Service. Successful efforts to prevent or delay the onset of NIDDM, and thus its toll on health, would have major health and economic consequences.

Genetics of Diabetes: Genetics appears to be the common denominator underlying the various factors that lead to diabetes. Intensified genetic research offers great promise for understanding, controlling, and preventing diabetes. Several NIDDK grantees were funded under the auspices of the Institute's recent initiative entitled "Genes for NIDDM." Their goal has been to conduct, in a coordinated fashion, detailed studies of the entire human genome in order to identify genes associated with NIDDM in families. In one collaboration, approximately 400 genetic markers for NIDDM have been examined in Mexican-American, African-American, and non-Hispanic white populations. Fifteen of these markers are significantly associated with NIDDM. The strategy now is to test the strength of these associations in independent population samples. Other grantees studying a Caucasian population discovered an association between an NIDDM gene and apolipoprotein A2. These studies are important because they demonstrate the ease with which new candidate genes can now be tested for the strength of their association with NIDDM susceptibility.

NIDDK grantees are collaborating with NIDDK intramural scientists in Phoenix to explore this question in the Pima Indian population. The intramural group has already identified a gene with a major effect on the age of onset of NIDDM in the Pima population. They also are exploring linkage between genetic markers and aspects of overt diabetes using a genome-wide search in this highly characterized population. In addition, NIDDK scientists in Phoenix, in collaboration with other investigators, have identified a mutation in the β_2 -adrenergic receptor gene that, although not itself associated with NIDDM, was associated with the early onset of diabetes in approximately 50 percent of the Pima Indian population of Arizona. The receptor also is thought to play a role in fat cell metabolism. Thus, the Institute's Phoenix field station and complementary extramural research projects represent a major example of research aimed at understanding complex genetic diseases.

Genes for diabetes have been examined in mice. Grantees cloned, sequenced, and fine-mapped the genomic region containing the *fat* gene, and found that it is very closely linked to a gene responsible for producing a protein involved in the processing of prohormones, such as proinsulin. Mice having a double-dose of this gene are unable to process normally a number of proteins, including insulin. The *fat* gene is the first example of an NIDDM gene in the mouse, and the first demonstration of an obesity-diabetes syndrome caused by a genetic defect in prohormone processing.

Diabetes in Minority Populations: Research has shown that the most prominent risk factors for NIDDM are a family history of diabetes, obesity, insulin resistance, hyperinsulinemia (increased insulin secretion), a history of gestational diabetes, and impaired glucose tolerance. African-Americans, Hispanic-Americans, and Native Americans are disproportionately affected by diabetes and its health complications. The U.S. Congress and the Department of Health and Human Services have highlighted the growing problem of diabetes in minority populations as an important public health issue deserving increased research effort.

As part of its continuing commitment to address this need, the NIDDK recently initiated the Diabetes Prevention Program, described previously. This major, seven-year clinical trial of preventive intervention strategies is targeted at individuals with impaired glucose tolerance, a history of gestational diabetes, and/or newly diagnosed NIDDM. Minorities will make up 50 percent of the study population. Interventions may include diet, exercise, and pharmacologic agents.

The factors involved in the disproportionate impact of NIDDM on minority populations are unclear, but probably include obesity and genetics. The tools of modern molecular biology now allow the systematic search for genes that are linked with various diseases, including NIDDM. Genetic studies are providing information useful to the eventual discovery of precise genetic defects responsible for NIDDM. The increased prevalence of NIDDM in minority populations is also associated with a greater prevalence of obesity. Most adults with diabetes, especially women in both Hispanic and African American populations are overweight. Additional studies are needed to determine whether weight intervention programs can prevent NIDDM and its complications.

Endocrinology

Hormonal Regulation of Bone and the Prevention of Osteoporosis: Bone is an organ with a dual purpose: to provide structural support for the body and to serve as a dynamic reservoir for important minerals, particularly calcium and phosphorus. Regulation of each of these functions depends on a balance of circulating and local hormones and growth factors, with imbalances resulting in diseases such as osteoporosis. Although all of the causative factors resulting in osteoporosis are not known, it is clear that several hormones play important roles, most notably estrogen, parathyroid hormone (PTH), calcitonin, and vitamin D. For postmenopausal women loss of estrogen results in accelerated and potentially severe loss of bone mineral. Whether this loss will lead to osteoporosis depends in part on how much bone mineral is originally built up by the young, growing skeleton, and for that PTH and the related hormone parathyroid hormone-related peptide (PTHrP), as well as calcitonin and vitamin D play important roles. NIDDK supported research has led to major advances in understanding the biologic roles of PTH, PTHrP, and their common receptor. In recent years, NIDDK grantees have isolated, cloned, and characterized each of these elements. Work is also underway to study how calcitonin and vitamin D interact with their receptors and how those receptors then signal bone cells to function.

NIDDK presently supports a number of small-scale clinical trials designed to test whether hormonal therapies can have a growth-promoting effect on bone. In one such clinical trial, investigators studied women with endometriosis treated with drugs to alleviate this condition which induces an early menopause, putting them at increased risk for osteoporosis. The investigators found the associated bone loss can be stopped and in some cases reversed through intermittent administration of PTH. Currently this trial is being expanded and others like it initiated to understand further the mechanism by which PTH promotes bone growth and its clinical utility for osteoporosis. In developing appropriate hormonal therapies, researchers are being guided by considerations of safety, ease of use, and long-term effectiveness.

In other basic studies, NIDDK-supported investigators have used state-of-the-art genetic approaches to create a mouse model lacking the gene for PTHrP or for the common PTH/PTHrP receptor. Striking results have implicated an important role for PTHrP in the initial development of bone. Studies have shown that for long bones both the receptor and the hormone are important to initial bone development and later maturation. This work has served as a stimulus for human studies as well. A human genetic disease, a form of short-limbed dwarfism, has now been found to be the result of a mutation in the receptor for PTH/PTHrP. The mutated receptor has been cloned and is now being used to better understand the mechanism of hormone action. As this basic research is continuously translated into human studies, new strategies for treatment and prevention of diseases of bone, such as osteoporosis, will emerge.

Hormones and Cancer: Most tissues of the body depend on circulating and local hormones and growth factors for their initial development as well as their day-to-day functioning. In breast tissue, the epithelial cells that line the milk ducts are dependent on a rich milieu of hormones. Estrogen and progesterone have well documented links to normal breast development and function, and to breast cancer; and recently insulin-like growth factor-I (IGF-1) and PTHrP have been implicated as well. To explore the roles of these hormones, NIDDK

supported investigators have used exciting new methods of gene targeting research to create mouse models in which the gene for either IGF-I or PTHrP has been "knocked-out."

In addition to its central role in reproductive function, estrogen has been linked to the risk of heart disease and osteoporosis and to stimulation of progression of breast cancers. These key roles played by estrogen have served to spur development of compounds with estrogen receptor agonist (stimulator) or antagonist (inhibitor) activity, in hope of identifying compounds with a favorable profile of action in the multiple tissues regulated by this hormone. NIDDK supported research has focused on understanding how estrogen and progesterone bind to their receptors and subsequently regulate cell growth and function. Knowledge gained by this basic research has helped to better understand how hormone antagonists work. Tamoxifen is the most widely used estrogen antagonist, but in some disturbing instances tamoxifen actually has an estrogen-like effect and contributes to dysfunctional tissue growth. NIDDK-supported research has pointed to ways in which different classes of hormone antagonists interact with the estrogen receptor and has identified model systems that can reveal how a particular antagonist will affect estrogen action. This research could very well speed the development of compounds which will have the desired blocking effect on estrogen-dependent tumors but allow for the positive effects of estrogen on bone and the cardiovascular system.

Neuroendocrine Regulation of Growth, Development, and Function: Pioneering work by investigators supported by NIDDK led to the explosion of research in the nascent field of neuroendocrinology in the early 1970s. The discovery of factors released from the brain, which in turn regulated the pituitary gland, was revolutionary in the development of our understanding of the coordinated regulation of bodily functions. This past year, NIDDK grantees discovered a new link in the regulation of response to stress and immune function. They uncovered a new hormone, called urocortin, which, it is thought, may be involved in a number of disorders that result in significant morbidity, such as depression, alcoholism, anorexia, and arthritis. This hormone appears likely to orchestrate many of the behavioral responses to stress and should stimulate the exploration for new therapies to combat the debilitating effects of stress.

Metabolic Diseases

As the lead Institute for cystic fibrosis (CF) research at the NIH, the NIDDK continues its commitment to develop new therapies and, ultimately, a cure for this most common lethal genetic disease in Caucasians which afflicts 30,000 Americans. The Institute also supports research on many other genetic metabolic diseases that individually affect as few as 100 to 1,000 people, but in aggregate comprise a substantial health burden and account for a large proportion of pediatric hospital admissions.

New Therapies for CF: Improved therapy has transformed CF from a disease characterized by death in early childhood to a chronic disease with most patients surviving well into adulthood. Until therapy directed at the basic molecular defect provides a cure, the pulmonary infection and inflammation that ultimately destroy lung tissue and kill most patients with CF are prime targets for therapy. Continued improvement in therapy directed at removing airway mucus and reducing infection and inflammation can preserve lung function until more definitive therapy is developed. An NIDDK-supported clinical trial has added an important new

pharmacologic approach to therapy. Ibuprofen, a nonsteroidal antiinflammatory drug widely used for arthritis, has been shown to significantly slow the rate of loss of lung function in CF. Thus, an inexpensive new treatment is effective in slowing progression of lung disease in CF patients.

In another NIDDK-supported study, three methods of sputum removal, including a new hand-held device called the Flutter, were compared in patients with CF. The quantity of sputum produced after 15 minutes use of the Flutter was more than three times that produced by either vigorous voluntary coughing or a 15 minute session of chest percussion and vibration by a respiratory therapist. This easy to use, inexpensive, portable device can significantly increase the independence of patients with CF, and has the potential to reduce health care costs, improve compliance with treatment, and enhance removal of mucus.

CF is characterized by persistent infection with a specific bacterial pathogen, *Pseudomonas aeruginosa*, which contributes significantly to the gradual decline in pulmonary function. A first step in infection is attachment of the bacteria to the lung surface by means of bacterial appendages called pili. NIDDK grantees now have identified the specific site of *Pseudomonas* binding to airway cells, and have determined that certain chemical characteristics of the CF lung cells enhance that binding, setting up a chain of events leading to inflammation and destruction of lung tissue. This work has important therapeutic implications for prevention or eradication of *pseudomonas* infection. Agents that prevent the binding of *Pseudomonas* to this receptor are under development.

Genetic Basis of Disease: About one in twenty Caucasians has a single copy of a mutant CF gene and one normal CF gene; these carriers have no symptoms of CF, but are at risk of having an affected child if they marry another CF carrier. Because such a high proportion of the population carries a single copy of the mutant gene, it has been suggested carriers may have a selective advantage or benefit which leads to increased survival and thus increased frequency of the mutant gene in the general population. The CF gene product regulates salt and water transport in the lungs, intestine, and bile, pancreatic and sweat ducts. While two mutant genes result in dehydrated, sticky secretions, investigators have found that, in animals, one mutant gene protects against secretory diarrhea due to pathogens such as cholera. These findings suggest that a single mutant CF gene may confer significant protection against pathogens causing secretory diarrhea and may account for the high (five percent) frequency of CF carriers in the Caucasian population.

Over the past year, the causes of several rare metabolic diseases have been determined. NIDDK-supported investigators have identified the genetic defect in a form of Zellweger Syndrome and the cloning of several genes that cause disorders of fatty acid oxidation. Identification of the genetic defect allows for the development of carrier testing and prenatal diagnosis for these diseases, as well as providing new approaches to treatments, such as enzyme replacement therapy and gene therapy.

Gene Therapy for Inherited Metabolic Diseases: Gene therapy remains a promising approach for the treatment of inherited metabolic diseases. However, as addressed by the Committee to Assess the NIH Investment in Gene Therapy, each of the currently used vectors

has deficiencies. For gene therapy to become a practical reality, improved gene therapy vectors need to be developed. The preclinical and clinical studies using adenoviral vectors have identified a new problem, the generation of immune responses to adenoviral proteins which result in transient expression of genes and preclude repeated administration of these vectors. Progress has been made toward modifying adenoviral vectors by deletion of additional viral genes to reduce host immune responses. NIDDK supported investigators have developed immunosuppressive regimens for co-administration with these vectors. These strategies are being tested in animal disease models, and are promising approaches to prolong expression of the corrective gene and permit repeated administration.

While adenoviral vectors were the first to be tested in phase one clinical trials for cystic fibrosis, there has been progress with several other gene delivery systems, including vectors based on adeno-associated virus, liposomes and DNA-conjugates. Phase one clinical trials using liposome-mediated gene therapy and adeno-associated viral vectors are now underway for cystic fibrosis.

Digestive Diseases and Nutrition

Digestive Diseases

Digestive diseases impact in a very major way on health in the United States. The 60 million digestive diseases reported each year result in 200 million days of curtailed activity, 50 million visits to physicians, 10 million hospitalizations, and nearly 200,000 deaths. It is expected that the estimated \$88 billion dollar economic burden of digestive diseases in 1992 is far greater today. NIDDK supports basic and clinical biomedical research and research training in the normal function and diseases of the gastrointestinal tract and associated organs.

Gallstones: Throughout the Western world, gallstone disease is a significant health and economic problem. Almost 12 percent of adults in the United States have gallstones, and more than 500,000 gallstone operations are performed yearly. The \$5 billion-associated cost for the treatment of symptomatic patients makes this disease the costliest of the digestive diseases. Thus, preventing gallstones from forming is an important goal. Gallstone prevalence increases with age, is more common in women than in men, and is also more common in American Indians and Mexican Americans. Among obese individuals, rapid weight loss is a particularly acute risk factor for developing gallstones and the most modifiable. It also has been observed that gallstones result from surgically-induced weight loss. A recently completed clinical trial conducted by NIDDK grantees, has established the optimal dose of a naturally occurring bile salt known as ursodeoxycholic acid to prevent gallstones in persons taking part in a very-low calorie diet program. A similarly designed trial by the same investigators evaluated the effects of ursodeoxycholic acid during weight reduction in patients having gastric bypass surgery. In both trials, either placebo or varied doses of the bile acid were used in treating the obese subjects. Both studies clearly showed that the prophylactic use of ursodeoxycholic acid at the optimal dose of 600 milligrams per deciliter is highly effective in preventing gallstone formation in patients having rapid weight reduction. The cost effectiveness of dissolving gallstones with this therapy has been shown not only during rapid weight loss, but in other high-risk periods such as following the birth of a child, and will potentially reduce the costs associated with treating

gallstones and their complications. Extending the use of ursodiol therapy to other high risk groups, developing further preventive strategies and a better understanding of the mechanisms involved will be the focus of future research.

Inflammatory Bowel Disease (IBD): Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, are extremely complex disorders and represent the major cause of morbidity from intestinal illnesses. While the exact pathogenesis of the diseases is poorly understood, scientific evidence has shown that interactions between the immune system, genetic susceptibility, and the environment are strongly implicated. In recent years, unprecedented developments in molecular biology have permitted creation of a new class of rodent models of intestinal inflammation that more closely resemble IBD in humans. These techniques now make it possible to over express or delete selected genes in rodents. For example, a transgenic rat model develops small and large bowel inflammation as well as arthritis and iritis. Other models contain certain gene deletions and thus are referred to as "knock out" mice. One of these models develops inflammation of the colon and another develops inflammation of the entire intestinal tract. A third model containing a mutated T cell receptor develops chronic intestinal inflammation without ulcers, while a fourth model minus a G protein develops colonic inflammation and adenocarcinoma. It would appear that the genetically determined susceptibility to chronic intestinal inflammation found in multiple models is likely present in humans. Available technologies allow investigators to identify the genes involved in such susceptibility. Bacterial flora also seem to play a crucial role in chronic IBD in these models. The instigation of chronic inflammation by bacterial flora and the absence of disease in germfree animals provide direct evidence of the crucial role played by enteric bacterial flora in chronic IBD. Another important finding is that the careful regulatory balance between pro- and anti-inflammatory cells of the immune defense system must be maintained to avoid stimulating destructive inflammatory events. Development of these new genetic models affords the opportunity to sort out in future studies the differences in background genes and the specifically altered genes to identify the factors that influence intestinal novel immunologic approaches, such as gene therapy, and in discovering the mechanisms involved in current pharmacologic therapies used to treat IBD.

***Helicobacter pylori* in Gastrointestinal Diseases:** The disease association between *H. pylori* and gastritis and duodenal ulcers is now well established. Infection with this bacterial organism is also a risk factor for gastric cancer. These findings were endorsed in 1994 by an NIH consensus development panel and have since mobilized the medical community to mount a major educational campaign directed at professionals and the lay public on a management strategy for peptic ulcer disease. At the core of treatment of this disease is the eradication of *H. pylori* with antibiotics and acid blockers which significantly reduce its recurrence. One question still baffling to researchers, however, is why only a small number of individuals become ill of the many who are infected with *H. pylori*. Recent work of NIDDK grantees has revealed that persons who acquire *H. pylori* very early in life are at increased risk for developing gastric cancer and gastric, but not duodenal, ulcer. These researchers also explored differences in *H. pylori* strains. It is believed that, while host factors including smoking, blood type O, and male gender, are known to predispose individuals to developing peptic ulcers, specific virulence factors of *H. pylori* strains may also influence the outcome of infection. The investigators discovered that persons infected with *H. pylori* strains of the CagA type have increased risk of

developing cancer or duodenal ulcer. The Cag A gene is present in 60 percent of *H. pylori* strains. Evidence also emerged that persons infected with strains of vacA genotype S1 type are at increased risk of having duodenal ulceration. VacA is the *H. pylori* gene which encodes a toxin that induces vacuolation of the cell cytoplasm. The understanding that stomach ulcers and some stomach cancers are caused by this bacterium presents major opportunities for future research to investigate what determines that certain strains of the bacteria are more virulent than others and to identify persons at highest risk for bad outcomes of infection. Avenues are also open to develop new therapies and possibly vaccines to prevent these diseases. It has already been estimated that \$400-800 million annually can be saved by preventing ulcer recurrence alone. Although worldwide rates of gastric cancer are declining, it remains a common and fatal cancer outside of the United States. Estimates are that as many as 60 percent of all gastric cancers could be prevented by control of this bacterium, which makes research in this area an important public health priority.

Gene Therapy in Liver, Biliary, and Pancreas Diseases: Recent investigations have resulted in development of improved technologies for gene transfer providing new avenues for definitive therapy of genetic and acquired diseases. For liver and biliary disease, gene therapy techniques have genetically modified the liver cell using a viral vector to infect cells and transfer new genetic material in a safe, specific and efficient manner. Recent studies have produced a first generation adenovirus that is devoid of certain regions of the virus genome and capable of infecting many different cell types. While the vector can express the introduced gene, it cannot fully replicate. When first-generation recombinant adenovirus vectors are directly infused into the blood, they basically target liver cells. In an attempt to circumvent an immune response to viral infection and toxicity to non-targeted tissues, a second-generation adenovirus vector also has been deployed. This technology has been utilized successfully in an animal model with an enzyme deficiency disease effecting a complete metabolic correction and reduced liver inflammation. The vector introduces a temperature sensitive replication mechanism, which prevents the virus from replicating at physiologic temperatures and thus makes it less immunogenic. Viral vectors can be targeted to specific cellular receptors as a means of achieving a high level of tissue specificity in gene therapy of liver disease. In an animal model for hepatitis B infection, targeted gene therapy techniques were coupled with antisense molecules technology and showed efficacy. Animals with acute hepatitis B infection were injected intravenously with specific cellular-targeted complexes coupled with antisense molecules, and hepatitis viral replication in infected liver cells was inhibited. The feasibility of the adenovirus vector system for gene transfer in pancreatic cells was also examined. These studies demonstrated that adenovirus is very efficient at transfecting pancreatic acinar cells with greater than 90 percent of the cells transfected. The ability to genetically manipulate normal pancreatic cells represents a major breakthrough in pancreatic research. Future gene therapy studies will focus on circumventing problems such as the immune response to viral infection and toxicity to non-targeted tissues in liver and biliary tract diseases. Other research will endeavor to optimize the condition for gene transfer of the pancreas.

Nutrition

The NIDDK is committed to fundamental nutrition research to expand our knowledge of nutrient function, the relationship of diet and nutrients to health and disease, and the prevention and treatment of diseases with nutritional components; especially through the application of the most current techniques in cell biology, molecular biology, immunology, and integrative physiology. The institute also is fostering clinical nutrition research in areas such as: obesity and eating disorders; the role of diet and physical activity in diabetes prevention and treatment; total parenteral nutrition; combined nutrient-drug interactions; and nutritional factors in chronic renal disease, end-stage liver disease, gastrointestinal dysfunction, metabolic disorders, and bone disease.

Obesity Genes: In FY 1995, extraordinary research progress began to unveil the molecular underpinnings of obesity. Building on the NIDDK-funded breakthrough discovery of an obesity gene, researchers have rapidly deciphered the actions of the gene's product. This protein is named leptin, from the Greek word *leptos*, meaning thin. Leptin is completely absent from the blood of the obese mice with the defective gene. Daily administration of a recombinant form of the missing leptin to these obese mice resulted in a 30 percent reduction in body weight in two weeks, due to significant decreases in food intake and increases in energy expenditure. Even normal mice receiving leptin showed reduced food intake and significant weight loss. These results, combined with other studies investigating obesity genes, provide strong evidence that leptin is a circulating hormone involved in regulating energy balance in mice.

Leptin appears to serve a similar function in humans. In lean and obese humans, blood levels of the hormone are highly correlated with body mass index, a rough measure of fatness. It seems likely that the high levels of leptin in many obese individuals indicate the presence of a defect in their ability to respond to the hormone's signal that enough fat has been stored. When humans were placed on diets to lose weight, their plasma leptin levels fell dramatically, to between one-half and one-eighth of initial values. Since leptin exercises control of fat levels by affecting appetite and energy expenditure, this diet-induced reduction in leptin levels offers a biological explanation for the difficulty people experience in maintaining weight loss. Apparently, after dieting, decreased leptin levels provide a powerful molecular signal urging the individual to eat more and to conserve energy by decreasing physical activity or increasing the efficiency of the activity.

In early 1996, another piece of the puzzle was revealed. The receptor for leptin in mice and rats has been identified, and appears to be identical with a gene that is associated with gross obesity and diabetes in rodents. This leptin receptor molecule appears to exist in several forms in the brain and other tissues, and is processed abnormally in a strain of obese diabetic mice. Researchers are investigating the human counterpart of this receptor gene, as well as its interactions with leptin.

Thus, in a single year, research starting with a fat mouse has discovered a new human hormone/receptor system that appears to be important in obesity. This in turn opens up a brand new research avenue focusing on the leptin/receptor mechanism and on specific pharmacologic agents that may affect the system — potentially leading to novel therapies for obesity and other

disorders of body weight regulation. Based on the new discoveries, it also may become possible to test for the genetic predisposition to obesity early in life. Once detected, dietary and physical activity modification could help to mitigate the adverse effects of predisposing genetic factors. Obesity prevention will be crucial in reducing the prevalence of many chronic diseases, including non-insulin-dependent diabetes, cardiovascular disease, certain cancers, gallstones, and stroke.

Ongoing Obesity Initiative: These discoveries relating to the genes for obesity are part of an ongoing NIDDK initiative that focuses on obesity as a total disease entity and a national public health problem. As part of this initiative, the Weight-Control Information Network (WIN) was established in 1994. In the past year, WIN has made great strides in its programs to communicate science-based information to the public. WIN is advised by the National Task Force on Prevention and Treatment of Obesity, which has convened regularly since 1992 to provide advice to the NIDDK on obesity research directions and on appropriate science-based communications to the public and the health care community. Over the past year, WIN has developed and initiated a pilot program of obesity prevention in minority women. The project focuses on a community-based approach to lifestyle modification in these individuals, with the hoped-for additional benefit of influencing their children and other family members. Private institutions such as local radio stations, cable TV, restaurants and the YMCA, are working with the WIN in fostering the "Sisters Together: Move More, Eat Better" message. WIN materials are being directed to health professionals through a newsletter, *WIN Notes*, and an exhibit at professional meetings. *WIN Notes* provides a direct route for disseminating the latest obesity and nutrition research advances from individual research grants and from the NIDDK-supported programs of Clinical Nutrition Research Units (CNRUs) and Obesity/Nutrition Research Centers (ONRCs).

Bionutrition: As the major locus for support of basic research in nutrient metabolism and energy expenditure at the NIH, the NIDDK provides the means for collaborative ventures throughout the NIH to encourage state-of-the-art nutrition research. In FY 1995, the Institute, through its leadership of the Division of Nutrition Research Coordination, succeeded in bringing a trans-NIH bionutrition RFA to fruition. This RFA, focussed on nutrient modulation of cell repair and maintenance of cell integrity, was highly successful. Nine of the NIH institutes and the Office of Research on Minority Health in the Office of the Director, NIH, funded grants through the initiative. Overall, 25 grants were funded in diverse areas, and several outstanding new investigators were attracted to the nutrition research field.

Anorexia is another bionutrition research field being encouraged through NIDDK leadership. Loss of appetite is observed in association with many disorders, including AIDS; end-stage cardiac, renal and liver disease; cancer; tuberculosis; some eating disorders; and major depressive disorders. It often also is observed in the elderly. Six NIH institutes now are cosponsoring a new program announcement in the pathophysiology of anorexia in disease and aging. This announcement will encourage submission of studies relating to primary endocrine, metabolic, and cellular mechanisms of anorexia, the role of the neural system and alterations of taste and smell in the condition, as well as its association with behavioral factors.

A revealing example of how bionutrition research can advance treatment options is the case of the role of glutamine in nutrition and cellular integrity. Glutamine is the most abundant amino acid in humans and for many years was considered to be non-essential in the diet. However, recent research has established that during severe illness, injury, or major surgery glutamine levels may decline to the point where insufficient glutamine is available to meet the body's wide range of needs for this nutrient. A number of studies have noted clinical responses due to providing glutamine in such situations. Of particular interest was a bone marrow transplantation study that documented a 7-day decrease in hospital stay among patients receiving intravenous glutamine supplements during their recovery from transplantation. This was associated with a per patient saving of over \$10,000. In FY 1995, new results linked the role of glutamine with that of the growth factor IGF-1. In animal studies of short bowel syndrome, greater intestinal growth occurred when glutamine and IGF-1 were administered jointly than when either was provided separately. Future studies will investigate the implications of this observation for humans and will continue to examine the importance of nutrient interactions with growth factors in human health and disease.

Kidney, Urologic, and Hematologic Diseases

The Kidney, Urologic, and Hematologic Diseases program of the NIDDK has primary responsibility at the National Institutes of Health for extramural research and research training in kidney, urologic, and fundamental aspects of hematologic diseases.

Kidney Diseases

NIDDK-supported research on diseases of the kidney focuses largely on preventing or delaying the progression of disease to end-stage and on improving the quality of life of those individuals who do have end-stage renal disease (ESRD). According to the U.S. Renal Data System, more than 240,000 people in the United States were treated for ESRD in 1992, at a direct medical cost of more than \$9.47 billion. The most frequent causes of ESRD include the kidney disease of diabetes mellitus, hypertension-related kidney disease, immune disorders causing inflammation of the kidney, and cystic kidney diseases.

Kidney Disease of Diabetes Mellitus (KDDM): Diabetes is the leading cause of kidney failure in the United States, accounting for 36 percent of all new ESRD cases. Researchers have been focusing on the mechanisms involved in the hallmark of KDDM -- the scarring of the kidney's filtering system, the glomeruli. The goal of such research is to find early processes that can be arrested before debilitating kidney damage occurs. A number of factors that are characteristic of the diabetic milieu, including glucose, angiotensin II, intraglomerular pressure, and a variety of growth factors, have been shown to contribute to the kidney scarring. This year, investigators studying the regulation of glucose uptake and metabolism within the kidney found evidence suggesting that a metabolic mechanism involving altered expression of a glucose transporter protein, GLUT4, possibly contributes to the increased glomerular filtration rate and glomerular pressure often observed early in the course of diabetes, before scarring becomes severe. If confirmed, this finding offers another possible target for arresting or delaying the development of KDDM. Other studies this year indicated that insulin may exert a direct effect on the kidney and that insulin-like growth factor may affect the scarring process. Scientists also

continue to investigate how the angiotensin-converting enzyme inhibitor enalapril affects the kidney at the molecular level, since enalapril was found to slow the progression of kidney disease in patients with insulin-dependent diabetes mellitus and may provide clues for new KDDM therapies.

Kidney Disease and Hypertension: Hypertension is the second leading cause of ESRD in the United States and is the leading cause among African Americans. The NIDDK-supported African American Study of Kidney Disease and Hypertension (AASK) is collecting data to compare the effects of three classes of antihypertensive medication and two levels of blood pressure in preventing kidney disease. This trial, also supported by the NIH Office of Research on Minority Health, involves participation by all U.S. medical schools with a predominantly African American student body and many major metropolitan hospitals with predominantly African American patient populations. NIDDK also supports basic research on hypertension-related kidney disease, including further studies of a gene identified last year in relation to a rare, inherited form of hypertension called Liddle's syndrome. NIDDK grantees linked Liddle's syndrome to a gene that encodes a subunit of the epithelial sodium channel. Mutations in that gene increased sodium reabsorption in the kidney. Because of its role in sodium reabsorption, this gene is thought to be a strong candidate for involvement in more common forms of hypertension.

Immune Disorders and Kidney Disease: Several kidney diseases are related to underlying disorders of the immune system. These diseases, which include IgA nephropathy, lupus nephritis, Goodpasture syndrome, Wegener's granulomatosis, Heymann's nephritis, and HIV nephritis, have in common an inflammation of the glomeruli and constitute the third leading cause of ESRD in Americans. Areas of research include the identification of immunologic target antigens, interaction between antibodies and antigens of the glomerular cells, mechanisms by which inflammatory cells migrate into the kidney and effect damage, and the development of scarring in advanced disease. Recent advances include mouse models of Goodpasture syndrome and HIV nephritis, description of how anti-DNA antibodies enter cells and affect nuclear function in diseases such as systemic lupus erythematosus, and increased understanding of how IgA immune complexes (IgA-IC) initiate inflammation. IgA nephropathy is the most common primary chronic glomerulonephritis worldwide. The disease develops when IgA antibodies produced in response to a foreign antigen form immune complexes that localize to the glomeruli and initiate glomerular inflammation and injury. This year, researchers have developed an animal model that establishes the causal relationship between IgA-IC and renal dysfunction. They have also identified several factors, including the size of the IgA-IC, that may be involved in the deposition of the complexes in the kidney and in the subsequent kidney failure. The NIDDK supports a multicenter clinical trial to evaluate the efficacy of alternate-day prednisone, or fish oils versus placebo, for the treatment of IgA nephropathy in children, adolescents, and young adults.

Polycystic Kidney Disease (PKD): Cystic kidney diseases are the fourth leading cause of ESRD among Americans, and autosomal dominant PKD (ADPKD) is the most common hereditary kidney disease in the United States. Approximately 50 percent of ADPKD patients develop ESRD, while the remainder have massive distortion of their kidneys even though adequate kidney function allows them a normal life span. Areas of PKD research supported by

the NIDDK include genetics, mechanisms of cyst formation and growth, clinical manifestations and complications, and experimental models. The recent identification, cloning, and sequencing of the ADPKD gene have been responsible for a burst of activity in PKD research, and progress has been made in many of the areas under study. Proteins that may initiate or promote cyst development have been characterized; a possible role for apoptosis in the progressive loss of renal tissue in ADPKD has been elucidated; and potential medical therapies have been identified.

Acute Renal Failure (ARF): ARF may occur from many different causes, often as a reaction to certain drugs, including certain commonly used analgesics; as a result of exposure to environmental toxins; or following bacterial or viral infection. Hemolytic uremic syndrome (HUS), for example, may occur in children or adults as a result of ingestion of food contaminated with *E. coli* O157:H7 bacteria. It is the most common cause of acute renal failure in infants and children and is associated with long-term morbidity, including ESRD in some cases. The NIDDK is participating in the effort to expand research on HUS and is encouraging researchers to study questions related to the factors and mechanisms by which the bacterial toxin affects kidney function, possible early markers of HUS, and potential treatment to improve the immediate and long-term outcome of the disease.

Hemodialysis: Once an individual has ESRD, life depends on replacement therapy: either dialysis treatments or renal transplantation. Of the nearly quarter of a million Americans reported to have been treated for ESRD in 1992, about 70 percent were treated with dialysis. Over the past decade, research spearheaded mostly by the pharmaceutical and medical devices industries has led to improved hardware for dialysis and thus the possibility of providing a more efficient and potentially more adequate dialysis treatment. However, despite the more sophisticated equipment, patient mortality and morbidity continue to be unacceptably high, and little research to define optimum dialysis treatment has been done. In an effort to determine what constitutes optimum hemodialysis, the NIDDK is currently supporting a clinical trial to test whether a higher than conventional hemodialysis dose and/or high-flux membranes will reduce patient mortality and morbidity. Results from the trial are expected in 2001.

Urologic Diseases

Prostate Growth: Benign prostatic hyperplasia (BPH) affects nearly half of all men by age 50 and close to 90 percent of men by age 80. The number of diagnostic and therapeutic alternatives being developed to treat this disorder is rapidly increasing. These many alternatives will have a significant impact on U.S. health care expenditures. Identification and characterization of the factors that regulate normal prostate growth are an essential step toward progress in treating both BPH and prostate cancer, diseases that result from abnormal prostate growth. Current understanding of normal prostate growth is based on three major discoveries: that growth of the adult prostate is dependent on androgens from the testes; that the androgen testosterone must be metabolized to dihydrotestosterone to be active in prostate growth regulation; and that the action of androgens on the prostate can be blocked with estrogens. These discoveries, made from studies in rat and dog tissue, led to major breakthroughs in the treatment of both BPH and prostate cancer in humans. However, the available therapies are not effective in all people and have not effected cures. Research over the past year has shown that 5-alpha reductase, the enzyme involved in the conversion of testosterone to dihydrotestosterone,

is itself regulated in a tissue-specific and species-specific manner. This finding underscores the importance of pursuing studies of prostate growth in human prostate tissue, since results from other human tissues or from the prostate tissue of other animals may not be translatable to the human prostate. The NIDDK currently supports a clinical trial to test the effectiveness of two classes of drugs in treating BPH. Prostate tissue from this trial will be banked for use in basic research on normal and abnormal prostate growth. The NIH Office of Research on Minority Health has provided support for a center in the trial that focused on an urban minority population. It is hoped that this trial will provide insights into not only BPH, but also other diseases of the prostate, such as chronic prostatitis. In addition, the NIDDK will continue to encourage increased investigator-initiated research on the basic structure and function of the prostate.

Urologic Disorders of Women: While interstitial cystitis (IC), urinary incontinence (UI), and urinary tract infection (UTI) occur in both sexes, they are much more common among women. These chronic conditions account for significant numbers of costly doctor and hospital visits annually. Recently, the emphasis of research on IC, UI, and UTI has again turned to fundamental bladder studies, in an attempt to understand the complex relationships between bladder structure and bladder function. Two types of membranes were characterized this year that seem to have roles in strengthening and stabilizing the bladder surface and in allowing the bladder to expand and contract. The recent insights into the basic molecular architecture of the urinary bladder indicate that the bladder can no longer be considered a simple, tissue-lined sac that contracts and relaxes in response to bladder filling. It is now evident that the inner lining of the bladder is complex, that many interrelated elements contribute to the normal function of the bladder, and that there are many opportunities for defects to occur in this intricate system. The NIH Office of Research on Women's Health (ORWH) has been working with the NIDDK to support basic research into bladder function and IC. The NIDDK-supported IC Data Base, which is collecting information about patients with IC and their disease, should provide important clues about the kinds of research that might lead to an understanding of the causes and development of IC, as well as possible treatment strategies. Bladder specimens taken in conjunction with the IC Data Base will be banked for use in basic IC research.

Kidney Stones: It is estimated that ten percent of the U.S. population will form a urinary tract stone at some time. Statistics have shown kidney stones to be the second leading cause of urinary tract complaints in people 15 to 64 years of age, with doctor and hospital costs for all ages amounting to more than \$1.3 billion. Most cases of stone disease are idiopathic, that is, there is no immediately identifiable cause for the occurrence of the stones. Most of these cases are chronic, with several occurrences of stone formation. Recent studies by NIDDK-supported investigators are providing insights into factors that might be involved in "idiopathic" stone formation, with the goal of preventing stones in people at risk. Areas of research include the mechanisms by which stone crystals in the urine are deposited in the kidneys, gender differences in stone formation, and naturally occurring factors that protect certain people from stone formation. Continuing studies on inhibitors of stone formation, such as uropontin and nephrocalcin, may lead to the development of effective drugs to prevent the recurrence of kidney stones.

Hematologic Diseases

Blood disorders, including hemoglobinopathies such as sickle cell disease and Cooley's anemia, cause significant morbidity and mortality. In addition, when anemia occurs secondary to a chronic disease such as renal failure, cancer, or AIDS, the management of both conditions is more difficult.

Sickle Cell Disease (SCD) and Cooley's Anemia: Researchers are continuing to refine efforts to develop drug treatments that can control the expression of hemoglobin genes in patients with SCD or Cooley's anemia. In addition to hydroxyurea, which has been shown to increase the production of fetal hemoglobin and thereby ameliorate the clinical course of SCD in some adults, other potential drugs are also under study. Among these are butyrate and acetate. Though both of these drugs have shown promise in small studies, they also show evidence of potentially dangerous toxic effects. Investigators hope that, as knowledge increases about the way these drugs work, it will be possible to design drugs with specific structural features that beneficially regulate the hemoglobin genes and without the features that lead to the toxic effects. Other studies of hemoglobin gene expression during fetal and postnatal development should also provide targets for the development of new drugs to treat hemoglobin diseases.

Red Blood Cell and Platelet Production: A large number of the factors regulating the formation of mature, circulating blood cells have been identified and studied extensively over the past several years. These include erythropoietin (which regulates production of red blood cells), interleukin-3 (basophils and megakaryocytes), GM-CSF (neutrophils, monocytes and basophils), G-CSF (neutrophils). For example, erythropoietin is considered a highly successful biotechnology drug, with over \$1 billion in sales worldwide. Last year, NIDDK grantees reported the identification of thrombopoietin, a long-sought growth factor that regulates the production of platelets. Continuing research to clarify the genetic control of these blood cell growth factors in the body should lead to clues about how blood cell production shuts down in certain diseases.

Research Centers

The NIDDK supports a total of 12 George M. O'Brien Kidney and Urological Research Centers, two Research Centers of Excellence in Pediatric Nephrology and Urology, and three Centers of Excellence in Molecular Hematology. These Centers provide a multidisciplinary environment for the study of many pressing problems in kidney, urologic, and hematologic research.

National Institute of Diabetes and Digestive and Kidney Diseases

Intramural Research

 Authorizing Legislation: Sections 301 and 487 of the Public Health Service Act. 1997

Authorization: Indefinite

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
399	\$81,433,000	417	\$86,791,000	417	\$86,657,000	—	-\$134,000

Nearly 250 research activities are under way in the NIDDK intramural research program at facilities in Bethesda, Maryland, and Phoenix, Arizona. Funding for the Intramural Research program during the last five years has been as follows:

	<u>Amount</u>	<u>FTE</u>
FY 1992	79,653,000	457
FY 1993	82,449,000	453
FY 1994	79,970,000	422
FY 1995	81,433,000	399
FY 1996	86,791,000	417

Rationale for Budget Request

The FY 1997 budget estimate for the Intramural research program is \$86,657,000, a decrease of .15 percent below the FY 1996 estimate of \$86,791,000 and the same level of FTEs. The fundamental research and clinical studies supported by the intramural research program help to provide a solid base of knowledge for the development of improved methods to treat and prevent disease. The following are examples of recent research achievements and activities of the NIDDK Division of Intramural Research.

Aging: NIDDK scientists evaluated the effect of administering recombinant human growth hormone (rhGH) and recombinant human Insulin-like Growth Factor-I (rhIGF-I), individually and in combination, on immune function in elderly rhesus monkeys. Their results demonstrated that both rhGH and rhIGF-I stimulate immune function, suggesting a causal relationship between short-term administration and an improvement in age-related immune dysfunction, as well as a clinical role for these hormones in states of immune compromise.

Anesthesia: Inhalational anesthetics remain the mainstay of clinical anesthesia, despite a narrow margin of safety that is attributable in a large part to the depression of cardiovascular function. NIDDK researchers have shown that isoflurane, a commonly used inhalational

anesthetic, works on a particular type of receptor in the brain and that one day it can likely be made much safer. In standard practice, isofluorane is a mixture of its mirror images. The investigators found that the anesthetic effects of one form of isofluorane were greater, providing strong evidence that isofluorane acts on a cell receptor. With lower doses of the pure form of isofluorane required to achieve the desired level of anesthesia, cardiac depression would be reduced.

Cancer-Related Research: In a recently completed Phase III trial, recombinant human thyroid-stimulating hormone was found to be safe and effective for use with radioactive iodine in diagnosing residual cancer cells following surgical removal of the thyroid, almost as effective as conventional thyroid hormone withdrawal. Preclinical toxicology studies, in anticipation of subsequent human trials, are underway to test a chemical with a high affinity for sigma receptors which has been shown to be a promising imaging agent for the detection of human tumors by positron emission tomography or single photon emission computed tomography scanning. NIDDK researchers are investigating the effect of IGF-I receptor antisense RNA in breast cancer cell growth and have found that expression of the antisense RNA directed against IGF-I receptor RNA lowers the expression of IGF-I receptors in certain breast cancer cells, which results in a reduction in the number of cell surface receptors and reduced cancer growth.

Diabetes: NIDDK researchers, in collaboration with other investigators, have identified a mutation in the beta₂-adrenergic receptor gene that, although not itself associated with non-insulin-dependent diabetes mellitus (NIDDM), was associated with the early onset of NIDDM in approximately 50 percent of the Pima Indian population of Arizona. In addition, the beta₂-adrenergic receptor is thought to play a role in fat cell metabolism.

Diabetes Treatment: Clinical studies show that IGF-I lowers blood sugar levels, along with cholesterol and triglyceride levels, in patients with non-insulin-dependent diabetes mellitus, particularly in those patients with insulin resistance. Additionally, these studies show that short-term use (overnight to one week) of IGF-I in patients with insulin-dependent diabetes could correct insulin resistance and help those patients severely out of control gain control over their diabetes.

Genetics of Diabetes: NIDDK scientists have undertaken a genome-wide search for anonymous DNA markers linked to insulin resistance in the Pima Indians. To date, over 500 markers have been typed on approximately 250 sibling pairs. Of particular interest was one marker which was linked to insulin action. This marker was located nearby another marker that has been linked to NIDDM. It appears, therefore, that there is a genetic element in this region contributing to insulin resistance and diabetes susceptibility. Efforts are now underway to clone this genetic element. In other studies, NIDDK scientists have identified a gene that was linked to insulin resistance. The gene encodes the intestinal fatty acid binding protein and a polymorphism in this gene results in an amino acid switch from alanine to threonine. Researchers found a significant association between the threonine encoding this protein genotype and insulin resistance.

Dopamine Receptors: Researchers have generated a mouse strain that lacks one of the subtypes of the dopamine receptor. This mouse model will be a powerful tool in studying the

linkage of the dopamine receptor to schizophrenia and Parkinson's and Huntington's diseases as well as studying hyperactivity disorders, particularly in children.

Drug Abuse: A promising compound has been identified and tested in monkeys for the treatment of cocaine abuse. In monkeys that were trained to self-administer cocaine and food, and worked equally for both, treatment with this compound decreased cocaine self-administration but not responding for food. This effect could be sustained for long periods, providing strong evidence that drugs can be developed to curtail cocaine abuse without altering "normal" behavior. Delta opioid receptors in the brain are also candidate targets for new drugs to mediate cocaine-seeking behavior, as well as tolerance and dependence to morphine and to regulate immune function. NIDDK scientists have recently synthesized a highly selective delta opioid ligand capable of crossing the blood-brain barrier. Derivatives of this ligand are expected to enable the study and quantitation of delta opioid receptors by positron emission tomography and single photon emission computed tomography scanning.

Gene Mapping: Gene maps show the locations of different genes on chromosomes and are important for the cloning of disease genes, for the diagnosis of genetic diseases and for research on how genes are switched on and off. In the past, NIDDK researchers described a novel way to cut a fragment of DNA from the human genome using a bacterial protein. Building on that technique, the scientists have now reported two new methods for the study of the human genome: one method allows for the amplification of a specific piece of DNA; the other enables scientists to join DNA segments to one another. Together, these techniques, which are less cumbersome than those currently being used, could revolutionize the process of physical gene mapping.

Generalized Thyroid Hormone Resistance (GTHR): NIDDK researchers have successfully developed a transgenic mouse model bearing the mutant thyroid hormone receptor associated with GTHR. These mice manifest two features typical of the human disease: attention-deficit hyperactivity disorder and a reduced weight. Studies of these animals are now possible and should provide novel insight into the pathogenesis of this disease. In other studies, NIDDK scientists have recently developed a new molecular diagnostic method for testing DNA from affected patients.

Insulin Action: NIDDK researchers have generated a mouse model that lacks insulin receptors in hopes of answering the question of whether both metabolic and growth-promoting actions of insulin are mediated by the insulin receptor. These mice are born with normal features but develop lethal metabolic abnormalities hours after birth, indicating that, in mice, insulin receptors mediate the metabolic actions of insulin but not the growth-promoting effects of insulin in fetal life.

Kidney Disease of Diabetes Mellitus: NIDDK scientists are currently exploring the linkage between nephron number, glomerular size and glomerular scarring by examining two different strains of mice. Data from recent studies indicated that glomerular size, but not glomerular scarring, correlated with nephron number, suggesting that an increase in glomerular volume may be associated with, but not sufficient for, the development of glomerular scarring. In other studies, NIDDK researchers used two different strains of mice to test whether a mutant

form of growth hormone might block diabetic kidney disease in these strains of mice. Data suggested that the development of diabetic kidney disease requires functional growth hormone.

Liver Disease: Basic research in the NIDDK intramural program led to double-blind, multicenter clinical trials of flumazenil, a drug that can correct severe brain dysfunction resulting from liver damage. NIDDK researchers showed that the confusion or coma that can accompany liver damage occurs when elevated levels of naturally occurring sedatives called benzodiazepines increase in the brain and peripheral tissues. Their studies indicated that the condition could be corrected by treating patients with drugs that block receptors for the benzodiazepine sedatives. In open-trial European studies that followed these findings, a majority of patients who were treated with flumazenil showed improved brain function. The multicenter trials of the drug showed similar results, and, with FDA approval, this treatment is likely to become an important means of controlling a severe, life-threatening consequence of liver disease.

Mouse Model for Tay-Sachs and Sandhoff Diseases: Recently, NIDDK researchers established mouse models corresponding to Tay-Sachs disease and Sandhoff disease. Although the Tay-Sachs mouse model shows the pathological features typical of the human disease, the mice showed no neurological abnormalities. The Sandhoff mice, however, in addition to displaying the pathological features typical of the human disease, showed profound neurological disturbances. The differences between the two models also highlighted differences in the ganglioside degradation pathway between mice and humans, which might be useful in developing means to treat these diseases.

Obesity: Recently, NIDDK grantees have cloned the mouse obesity (*ob*) gene and identified a homologous human gene. As a step toward understanding the regulation of the *ob* gene, NIDDK intramural researchers have now cloned and sequenced the mouse *ob* promoter and have characterized its activity in expression assays in cultures of rat adipose cells. Studies of the regulatory mechanisms that control gene expression of the *ob* gene and of the promoter elements that allow for adipose specific expression will be important for understanding the regulation of body fat in the normal and pathological state.

Sickle Cell Disease and Beta-Thalassemia: Several years ago, a small NIDDK clinical study showed that hydroxyurea (HU), which increases fetal hemoglobin, was a good candidate drug for the treatment of hemoglobin disorders. Fetal hemoglobin, high at birth but decreasing thereafter, protects the newborn from the clinical manifestations of sickle cell disease. The investigators showed that HU increases fetal hemoglobin levels in patients with sickle cell disease, thereby reducing anemia. Those results have now been confirmed in a recent large, prospective multicenter study which showed that HU can improve the clinical course of sickle cell anemia in some adults. HU has also shown promise for the treatment of patients with beta-thalassemia. NIDDK researchers, in a recent study of HU effects in Chinese beta-thalassemia patients, demonstrated an improvement in the effectiveness of red blood cell production and relief from the clinical symptoms after several months of therapy.

Stroke: 1-Aminocyclopropanecarboxylic acid, a compound shown by NIDDK scientists to prevent brain damage following stroke in animals was shown to be safe in recently completed

human Phase I trials. Continuing studies of this drug at the NIDDK have recently indicated that the compound may also be useful for the treatment of spinal injury.

Structural Biology: NIDDK scientists have determined the solution structure of a specific complex of the DNA-binding domain of the human SRY (sex-determining region Y) protein using multidimensional nuclear magnetic resonance, in hopes of providing the framework for explaining the effects of clinical mutations at the molecular and atomic levels.

National Institute of Diabetes and Digestive and Kidney Diseases

Research Management and Support

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act, 1997

Authorization: Indefinite

FY 1995 Estimate		FY 1996 Actual		1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
173	\$25,832,000	173	\$24,041,000	173	\$23,936,000	—	-\$105,000

Support is provided through this activity for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, procurement, property control, and travel audit and control, which are most efficiently performed as centralized functions. Other functions included under this activity are review, management, and negotiation of research and development contracts of the categorical program areas, translation of scientific findings to the medical community and members of the public, and the establishment of program plans to emphasize scientific opportunities identified by the national biomedical research community.

Funding for the Research Management and Support program during the last five years has been as follows:

	<u>Amount</u>	<u>FTE</u>
FY 1992	\$24,470,000	172
FY 1993	24,052,000	170
FY 1994	25,574,000	175
FY 1995	25,832,000	173
FY 1996	24,041,000	173

Rationale for the Budget Request

The FY 1997 request for Research Management and Support is \$23,936,000 and an employment level of 173 FTEs. This is a decrease of \$105,000 and provides the same level of FTEs as the FY 1996 level.

A major portion of the resources of this activity is devoted to review and approval of grants functions, including professional support personnel who are responsible for the administration of the Institute's grant activities. The staff assists in the planning and development of programs in research and training that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; reviews and

evaluates research and training grant applications for presentation to the NIDDK Advisory Council and provides required Council staff assistance; and serves as liaison with applicants, grantees, other components of NIH and the Department, and interest organizations.

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National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects						
Noncompeting.....	1,536	\$357,165,000	1,668	\$412,877,000	1,551	\$376,748,000
Administrative supplements.....	(175)	10,856,000	(41)	1,595,000	(41)	1,643,000
Renewal.....	287	68,048,000	210	55,769,000	304	80,798,000
New.....	287	54,487,000	236	45,253,000	335	68,693,000
Supplemental.....	1	20,000	(8)	(2,144,000)	1	22,000
Subtotal, competing.....	565	122,555,000	438	98,878,000	640	147,513,000
Subtotal, RPGs.....	2,101	490,576,000	2,106	513,350,000	2,191	525,904,000
SBIR/STTR.....	75	11,604,000	60	11,865,000	70	11,833,000
Subtotal, RPG.....	2,176	502,180,000	2,166	525,015,000	2,261	537,737,000
Research Centers						
Specialized/Comprehensive centers.....	59	52,473,000	59	52,161,000	59	52,161,000
Other Research						
Research Career Program.....	208	17,423,000	210	18,328,000	216	18,828,000
Minority biomedical research support.....	0	1,720,000	0	1,794,000	0	1,848,000
Other research related.....	28	2,286,000	30	2,014,000	30	2,074,000
Subtotal, other research.....	234	21,429,000	240	22,136,000	246	22,750,000
Total, research grants.....	2,469	576,082,000	2,465	599,312,000	2,566	612,648,000

Training					
Individual awards:					
Noncompeting.....	96	2,795,000	78	2,288,000	84
Competing.....	104	2,855,000	88	2,417,000	82
Subtotal, Individual.....	200	5,650,000	166	4,685,000	166
Institutional awards:					
Noncompeting.....	499	18,046,000	511	16,424,000	514
Competing.....	230	7,022,000	249	7,616,000	246
Subtotal, Institutional.....	729	23,068,000	760	24,040,000	760
Total, training.....	929	28,718,000	926	28,725,000	926
Research and development contracts (SBIR/STTR).....					
	35	12,909,000	45	20,648,000	42
	(6)	(696,000)	(5)	(2,000,000)	(5)
FTEs					
Intramural research.....	399	81,433,000	417	86,791,000	417
Research management and support.....	173	25,832,000	173	24,041,000	173
Total.....	572	724,974,000	590	759,517,000	590
Clinical Trials					
		(57,081,000)		(59,200,000)	
					(61,800,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(Dollars in thousands)

	1993 Actual FTEs Amount	1994 Actual FTEs Amount	1995 Actual FTEs Amount	1996 Estimate FTEs Amount	1997 Estimate FTEs Amount	Change FTEs Amount
Extramural Research:						
Diabetes, Endocrinology and Metabolism.....	\$275,665	\$284,591	\$304,635	\$319,960	\$326,720	+6,760
Digestive Diseases and Nutrition.....	137,959	139,947	145,092	152,342	155,550	+3,208
Kidney Disease, Urology and Hematology.....	153,743	163,677	167,982	176,383	180,112	+3,729
Subtotal, Extramural.....	567,567	588,215	617,709	648,685	662,382	+13,687
Intramural Research.....	453	422	399	417	417	—
Research management and support.....	170	175	173	173	173	—
Subtotal obligations.....	623	597	572	590	590	—
Unobligated Balance Lapsing.....	158	432	23	—	—	—
Total, Budget Authority.....	623	597	572	590	590	+13,458

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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National Institutes of Diabetes and Digestive and Kidney Diseases

Summary of Changes

1996 Estimated budget authority.....	\$759,517,000
1997 Estimated budget authority.....	<u>772,975,000</u>
Net change.....	+13,458,000

	1996 Current Estimate Base Budget (FTEs) Authority	Change from Base Budget (FTEs) Authority
Changes:		
A. <u>Built-in:</u>		
Intramural Research:		
a. January 1997 pay increase.....	35,530,000	+ \$815,000
b. Annualization of January 1996 pay increase.....	35,530,000	+226,000
c. Within-grade increase.....	35,530,000	+474,000
d. FECF and Unemployment Compensation.....	35,530,000	+7,000
e. Cost of centrally furnished services.....	22,959,000	-213,000
f. Increased cost of service and supply fund.....	14,671,000	+323,000
g. Increased cost of supplies and materials.....	13,631,000	+300,000
Subtotal.....		<u>+1,932,000</u>
Research Management and Support:		
a. January 1997 pay increase.....	11,721,000	+270,000
b. Annualization of January 1996 pay increase.....	11,721,000	+74,000
c. Within-grade increase.....	11,721,000	+192,000
d. Increased cost of centrally furnished services.....	5,370,000	-106,000
e. Increased cost of service and supply fund.....	3,590,000	+79,000
f. Increased cost of supplies and materials.....	3,360,000	+74,000
Subtotal.....		<u>+583,000</u>

Summary of Changes - continued

	1996 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
B. Program:				
Increase:				
1. Research project grants				
a. Noncompeting.....	1,668	414,472,000	(117)	-36,081,000
b. Competing.....	438	98,878,000	202	+48,635,000
c. SBIR/STTR.....	80	11,665,000	10	+168,000
Total.....	2,166	525,015,000	95	+12,722,000
2. Other research.....	240	22,136,000	8	+614,000
3. Training.....		28,725,000		+861,000
4. Research and development contracts.....	45	20,648,000	-3	-500,000
5. Intramural Research.....	417	86,791,000		-2,066,000
6. Research Management and Support.....	173	24,041,000		-688,000
Subtotal.....				+10,943,000
Total changes.....				+13,458,000

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National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Object

	<u>FY 1996</u> <u>Estimate</u>	<u>FY 1997</u> <u>Estimate</u>	<u>Increase</u> <u>or</u> <u>Decrease</u>
Total compensable workyears:			
Full-time equivalent employment.....	590	590	0
Full-time equivalent of overtime and holiday hours.....	3	3	0
Average ES salary.....	114,043	116,424	+2,381
Average GM/GS grade.....	10.5	10.5	0
Average GM/GS salary.....	50,124	51,575	+1,451
Average salary, grades est. by act of July 1, 1944 (42 USC 207).....	83,570	86,077	+2,057
Average salary of ungraded positions.....	56,475	58,169	+1,694
Personnel Compensation:			
Permanent Positions.....	\$23,500,000	\$24,517,000	\$1,017,000
Positions other than permanent.....	6,737,000	7,020,000	+283,000
Other personnel compensation.....	1,496,000	1,561,000	+65,000
Special personnel service compensation.....	7,685,000	8,018,000	+333,000
Total, personnel compensation.....	39,418,000	41,116,000	+1,698,000
Personnel benefits.....	7,798,000	8,130,000	+332,000
Benefits for former personnel.....	35,000	40,000	+5,000
Travel and transportation of persons.....	1,000,000	1,000,000	0
Transportation of things.....	215,000	220,000	+5,000
Rental Payments to Others.....	50,000	50,000	0
Communications, Utilities & Misc.....	1,900,000	1,900,000	0
Printing and Reproduction.....	650,000	650,000	0
Other Services:			
Consulting services.....	250,000	250,000	0
Other services.....	3,453,000	3,452,000	-1,000
Purchases from Gov't accounts.....	37,451,000	35,685,000	-1,766,000

Budget Authority by Object - Cont'd

Operation and maintenance of facilities	1,800,000	1,800,000	0
R&D Contracts	15,948,000	15,448,000	-500,000
Operation and maintenance of equipment	1,350,000	1,350,000	0
Substance and support of persons.....	3,500,000	3,500,000	0
Supplies and materials	9,717,000	9,505,000	-212,000
Equipment	6,800,000	6,500,000	-300,000
Grants, Subsidies and Contributions.....	628,037,000	642,234,000	+14,197,000
Insurance claims and indemnities.....	<u>145,000</u>	<u>145,000</u>	<u>0</u>
TOTAL	759,517,000	772,975,000	+13,458,000

Note: Includes FTEs associated with HIV/ AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Administrative Costs
(Dollars in thousands)

	FY 1996 Current Estimate	FY 1997 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1).....	\$23,500,000	\$24,517,000	+1,017,000
Other than full-time permanent (11.3).....	6,737,000	7,020,000	+283,000
Other personnel compensation (11.5).....	1,496,000	1,561,000	+65,000
Special personal services payments (11.8)...	7,685,000	8,018,000	+333,000
Total, Personnel Compensation (11.9).....	39,418,000	41,116,000	1,698,000
Civilian personnel benefits (12.1).....	7,798,000	8,130,000	+332,000
Benefits for former personnel (13.0).....	35,000	40,000	+5,000
Travel (21.0).....	1,000,000	1,000,000	0
Rental payments to others (23.2).....	215,000	220,000	+5,000
Transportation of things (22.0).....	50,000	50,000	0
Communications, utilities, and			
Miscellaneous Charges (23.3).....	1,900,000	1,900,000	0
Printing and reproduction (24.0).....	650,000	650,000	0
Consulting Services (25.1).....	250,000	250,000	0
Other services (25.2).....	3,453,000	3,452,000	-1,000
Purchases from Gov't Accounts (25.3).....	31,294,000	29,528,000	-1,766,000
Operation & Maintenance of			
of Facilities (25.4).....	1,800,000	1,800,000	0
Operation & Maintenance of			
of Equipment (25.7).....	1,350,000	1,350,000	0
Subsistence and support of persons (25.8).....	3,500,000	3,500,000	0
Supplies and materials (26.0).....	9,717,000	9,505,000	-212,000
Total	102,430,000	102,491,000	+61,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTSFY 1996 House Appropriations Committee Report LanguageDiabetes

Diabetes - The House in its report 104-209, page 64 states that in light of the enormous financial and personal costs of diabetes, and given the new and promising gains in diabetes research, the Committee encourages NIDDK to redouble its efforts in research programs for diabetes. The Committee urges NIDDK to continue its current efforts to fund the genetic defects which are likely to be responsible for Type I diabetes and which may be the basis for vulnerability to diabetes and its complications in all cases.

Action Taken or to be Taken

The Institute has implemented the Diabetes Prevention and Treatment Initiative, which includes basic and applied research and two major clinical trials for the prevention of insulin-dependent and non-insulin dependent diabetes. Identification of genes associated with diabetes and, more importantly, determining the function of these genes, are high priority research areas. The NIDDK now is supporting two Diabetes Interdisciplinary Research Programs having a genetics focus. The Institute will attempt to further strengthen its diabetes genes portfolio through investigator-initiated grants.

Kidney Disease

Kidney Disease - The House in its report 104-209, page 64 states that the number of ESRD patients doubled between 1984-1991 and is expected to double again in the next seven years. Nephrology research such as the identification of genes critical to the delay of the progression of kidney failure in insulin-dependent diabetics is yielding promising results. The Committee is encouraged by these results and urges the Institute to provide strong research support that may lead to reductions in the burden and cost of kidney diseases.

Action Taken or to be Taken

HEMO, a multicenter clinical trial to determine whether a higher than usual dose of dialysis and high-flux dialyzers can significantly improve morbidity and mortality in hemodialysis patients, began in April of 1995. Specific parameters for approaches to many procedures were defined for the trial and, if successful, will become standards for dialytic therapy in the U.S.

Polycystic Kidney Disease

Polycystic kidney disease - The House in its report 104-209, pages 64 and 65 states that polycystic kidney disease (PKD) affects some 600,000 Americans....The Committee encourages NIDDK to continue its investment in this area.

Action Taken or to be Taken

NIDDK funding for PKD research has grown from \$1.4 million in FY 1986 to an estimated \$6.1 million in FY 1995. An RFA to support basic research on the mechanisms underlying PKD resulted in funding 18 new PKD-related grants in FY 1995. Applications are anticipated for interdisciplinary PKD research centers in response to a current RFA for George M. O'Brien Kidney Research Centers. Up to five highly meritorious Kidney Research Centers will be funded in FY 1997. The NIDDK also sponsored a scientific workshop in 1995 as an outgrowth of discovery and sequencing of the ADPKD1 gene, responsible for more than 80 percent of all PKD cases. The Institute will make every effort to fund additional PKD research within available resources.

Urological diseases

Urological diseases - The House in its report 104-209, page 65 states that the Committee is pleased with the continued growth of research on urological diseases. Diseases of the prostate are a significant health burden. The Committee encourages the NIDDK to continue its research in the basic science of prostate growth. The Committee is also concerned about the high prevalence of prostate disease in minority populations. In addition, the Committee urges the Institute to strengthen its research program on women's urological diseases by placing special emphasis on grants related to interstitial cystitis, urinary incontinence and urinary tract infections.

Action Taken or to be Taken

The NIH continues its research efforts in the basic and clinical science of prostate growth. To further cultivate research in the area, NIDDK will sponsor an International Symposium on Prostate Growth in March of 1996. The Institute also seeks to enroll a significant number of minority men in its Benign Prostatic Hyperplasia (BPH) Clinical Trial. Data on possible racial differences would provide valuable information on the incidence and clinical course of prostate disease. Additionally, the study will develop a bank of biopsy tissue for further research.

An RFA on disorders of the urinary bladder was issued in 1995. It is anticipated that seven to nine awards will be made in 1996.

Prostatitis

Prostatitis - The House in its report 104-209, page 65 states that the Committee has learned of the magnitude of the problems of prostatitis, which affects men in their twenties and thirties and becomes a lifelong disability. Yet, the Committee understands that little research is being done on this disease, and that there has been little progress in understanding and effectively treating it. The Committee encourages NIDDK to develop a research program in this area and to consider what steps are necessary to encourage greater interest in the disease in both the intramural and

extramural communities. The Committee would like the Director to be prepared to address these issues in the hearings on the 1997 appropriations.

Action Taken or to be Taken

The NIDDK sponsored a workshop on prostatitis in December 1995. Goals were to develop a clinical definition of chronic prostatitis and clinical research criteria as well as to identify future research needs. In addition, the NIDDK will be sponsoring an International Symposium on Prostate Growth. Major objectives of this symposium are to encourage new investigators to enter the field of prostate research and to elicit fresh ideas and opportunities for future studies.

Liver Disease

Liver Disease - The House in its report 104-209, page 65 states that the Committee heard testimony on the impact of hepatitis and other liver and gallbladder diseases, which affect 25 million Americans....The Committee encourages NIDDK to place an emphasis on liver disease research, with a particular focus on hepatitis C.

The NIDDK supports a vigorous research program in liver and gallbladder disease. Chronic hepatitis is the major indication for liver transplantation. Thus, the Institute is supporting state-of-the-art testing for hepatitis C virus (HCV) in patients who received liver transplants through the NIDDK Liver Transplantation Database. This testing will provide the best available information on HCV related to risk and course of disease in the liver transplant patient. The NIDDK and the NIAID will also sponsor a consensus development conference on chronic hepatitis C in 1997.

Nutrition

Nutrition - The House in its report 104-209, page 65 states that the Committee urges the NIDDK to continue its nutrition initiative and particularly its focus on obesity and on clinical research in nutrition....The Committee remains supportive of the clinical nutrition research unit and obesity and nutrition research centers programs.

Action Taken or to be Taken

NIDDK is continuing to fund its Clinical Nutrition Research Units (CNRU) and Obesity Nutrition Research Centers (ONRC). In addition, a special focus is being maintained on obesity genes research. Emphasis on translation of science-based obesity information is occurring through the Weight Control Information Network (WIN).

Hemolytic Uremic Syndrome (HUS)

Hemolytic Uremic Syndrome (HUS) - The House in its report 104-209, page 65 states that the Committee encourages NIDDK to support research on HUS in order to develop effective treatments for the disorder.

Action Taken or to be Taken

The NIDDK currently supports HUS-related research projects that focus on the mechanisms of acute renal endothelial cell injury and possible therapeutic targets. The NIDDK recently released an RFA entitled "Hemolytic Uremic Syndrome: Pathophysiology and Treatment Interventions."

FY 1996 Senate Appropriations Committee Report Language

Diabetes

Diabetes - The Senate in its report 104-145, page 76 states that the Committee continues to be concerned about the extremely high incidence of diabetes among Native Americans, Native Hawaiians, and Pacific Islanders, particularly residents of the Commonwealth of the Northern Marianas Islands where as many as 50 percent are afflicted with diabetes. The Committee urges the Director to develop specific interventions targeted to high-risk populations such as these.

Action Taken or to be Taken

The NIDDK has implemented a major national clinical trial, called the Diabetes Prevention Program (DPP), which is using lifestyle and pharmacologic intervention strategies to prevent the onset of non-insulin-dependent diabetes mellitus (NIDDM) in people with impaired glucose tolerance or gestational diabetes mellitus who are at high risk for developing NIDDM. Since minority populations are disproportionately affected by diabetes and its health complications, approximately 50 percent of the patients enrolled in this study will be from minority populations. In addition, the NIDDK and the NIH Office of Research on Minority Health continue active collaborations in this area. The ORMH is providing major support for NIDDK activities: (1) the gestational diabetes and assessment of visceral adiposity components of the DPP; (2) the Pathogenesis of NIDDM in Mexican American Women study; and (3) the Diabetes Genes, Treatment, and Prevention in Minorities Research Initiative (co-funding several studies).

Liver Disease

Liver Disease - The Senate in its report 104-145, page 76 states that the Committee believes that greater emphasis needs to be placed on liver disease research and encourages the NIDDK to convene a conference of leading scientists to develop a national research agenda with specific recommendations for the Committee to consider next year.

Action Taken or to be Taken

The National Digestive Diseases Interagency Coordinating Committee met in December 1995 and agreed that the research goals set forth in the national agenda of the American Liver Foundation

(ALF) are in agreement with the multiple research missions of the Committee's membership. In December 1996 the NIDDK and NIAAA will co-sponsor a meeting on *Liver Transplantation for Alcoholic Liver Disease*. A consensus development conference for chronic hepatitis C also will be held in the Spring of 1997, cosponsored by NIDDK and NIAID. The NIDDK is currently supporting testing for viral hepatitis in patients transplanted through the NIDDK's Liver Transplantation Database contract.

The NIDDK is currently supporting testing for viral hepatitis in patients transplanted through the NIDDK's Liver Transplantation Database contract.

Urological Diseases

Urological Disease - The Senate in its report 104-145, page 77 states that the Committee is pleased with the continued growth of research on urological diseases. Diseases of the prostate are a significant health burden. Funds have been provided to increase new research grants in the basic science of prostate growth utilizing the tissue resources available from the ongoing clinical trial. The Committee continues to acknowledge the importance of establishing a prostate disease data base. Insufficient attention is being directed to women's urological health. The Committee urges that the Institute, working with the Office of Research on Women's Health, to expand its research program on women's urological diseases by placing special emphasis on grants related to interstitial cystitis, urinary incontinence and urinary tract infections. The Committee is concerned about the high prevalence of prostate disease in minority populations. The Committee directs the Interagency Coordinating Committee for Urological Diseases to develop a joint plan to expand research in this area and include this plan in its annual report.

Action Taken or to be Taken

The NIH continues its research efforts in the basic and clinical science of prostate growth. The NIDDK will sponsor an International Symposium on Prostate Growth in March of 1996.

A goal of the NIDDK-sponsored Benign Prostatic Hyperplasia (BPH) Clinical Trial is to enroll a significant number of minority men with BPH. The study will develop a bank of biopsy tissue for which clinical and demographic data are known that can then be used for further research studies.

The NIDDK issued an RFA in March of 1995 entitled "Basic and Epidemiologic Research Related To Disorders of the Urinary Bladder." It is anticipated that the NIDDK will make seven to nine awards in 1996.

The NIDDK is convening a subgroup of the Urology-Interagency Coordinating Committee, with representatives from the NIDDK, NCI, NIA, ORMH, and the extramural community to plan an initiative to address Prostate Disease in Minorities. The first phase of this initiative will be a workshop, to be held in the fall of 1996.

Irritable Bowel Syndrome

Irritable Bowel Syndrome - The Senate in its report 104-145, page 78 states that the irritable bowel syndrome (IBS) is a chronic complex of disorders that malign the digestive system, affecting 35 million people annually. These common dysfunctions strike people from all walks of life and result in a significant toll of human suffering and disability. The Committee is concerned about the

increasing frequency of IBS and the adverse impact these disorders have on the quality of life and health care expenditures of those afflicted. The Committee recommends that NIDDK provide adequate funding for irritable bowel syndrome/functional bowel disorders research and be prepared to report on the feasibility of developing comprehensive IBS education initiatives during the fiscal year 1997 budget hearings.

Action Taken or to be Taken

IBS is a compelling area of research. The NIDDK is currently funding a large-scale clinical study to compare clinical treatments for chronic, painful functional bowel disorders that predominately affect women. This study should provide clinicians with predictors of success among types of IBS patients and types of therapy that will improve symptoms and quality of life and reduce attendant health care costs. The Institute-supported National Digestive Diseases Information Clearinghouse provides an information packet on IBS with the aid of the NIDDK Combined Health Information Database. As professional and patient advocacy groups move toward unifying research and education efforts, scarce federal research dollars can be made available for the basic and clinical research that will result in greater understanding of the underlying causes and treatment of these disorders.

Prostatitis

Prostatitis - The Senate in its report 104-145, page 78 states that the Committee has received information concerning the problem of prostatitis, which leaves men in their twenties and thirties with a lifelong disability. The Committee understands that little research is being supported on understanding and treating prostatitis and encourages the NIDDK to take steps to develop a plan to stimulate and support research on this problem. The Committee expects the Director will be prepared to report on the Institute's plans for prostatitis during the regular budget hearings for fiscal year 1997.

Action Taken or to be Taken

The NIDDK is actively encouraging scientific investigators to apply for research grants in prostatitis. A workshop on prostatitis sponsored by the Institute in December of 1995 focused on developing a clinical definition of prostatitis, clinical research criteria, and concepts for future research. NIDDK will also sponsor an International Symposium on Prostate Growth directed at the molecular and cellular aspects of regulation of normal and abnormal prostate growth.

NATIONAL INSTITUTES OF HEALTH
National Institutes of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U. S. Code Citation	1996 Amount Authorized	1996 Appropriation	1997 Amount Authorized	1997 Budget Request
Research and Investigation.....	Section 301	42&241	Indefinite		Indefinite	
				\$730,792,000	>	\$743,388,000
National Institute of and Digestive and Kidney Diseases.....	Title IV, Part C	42&285	Such Sums as necessary		Authorization is pending	
National Research Service Awards.....	Section 487 (D)	42&241	Such Sums as necessary	\$28,725,000	Authorization is pending	\$29,586,000
				\$759,517,000		\$772,975,000
Total Budget Authority						

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Seque Allowance</u>	<u>Appropriation</u> 1/
1988	\$440,504,000	\$563,768,000 2/	\$549,784,000	\$534,733,000
1989	562,258,000 3/	546,902,000 4/	565,908,000	559,538,000
1990	577,235,000 5/	590,276,000	593,497,000	589,594,000 6/
1990 Sequester				-8,117,000
1991	605,349,000	613,686,000 7/	626,986,000	615,272,000 8/
1991 Sequester				-8,000
1992	658,557,000	667,820,000	652,861,000	659,538,000 9/
1993	699,809,000	688,633,000	688,633,000	681,342,000 10/
1994	677,135,000	716,054,000	716,054,000	716,054,000
1995 11/	731,500,000	726,784,000	728,784,000	727,628,000 12/
1995 Rescission				-679,000
1996	748,798,000 11/	759,517,000	738,456,000 11/	759,517,000
1997	772,975,000 11/			

1/ Reflects enacted supplementals, rescissions, reappropriations and reductions.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ The 1989 Request excludes funds for AIDS research and education (\$3,650,000) that has been proposed for consolidation at the Office of the Assistant Secretary for Health.

4/ Excludes \$25,509,000 in NRSA training programs not considered.

5/ The 1990 Request excludes funds for National HIV program (\$5,394,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ Excludes enacted administrative reduction of \$2,293,000.

7/ Excludes \$23,872,000 in NRSA training programs not considered.

8/ Excludes enacted administrative reductions of \$15,238,000 and \$1,762,000.

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- 9/ Excludes enacted administrative reductions of \$435,000 and \$4,107,000.
- 10/ Excludes enacted administrative reductions of \$7,291,000.
- 11/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
- 12/ Excludes enacted administrative reductions of \$656,000.

National Institute of Diabetes and Digestive and Kidney Diseases

Program Administration
Detail of Full-Time Equivalent Employment

	1995 Actual	1996 Estimate	1997 Request
Executive Level I.....			
Executive Level II.....			
Executive Level III.....			
Executive Level IV.....			
Executive Level V.....	2	2	2
Subtotal.....	2	2	2
Total - Exec. Level Salary...	\$205,143	\$210,354	\$215,882
ES-6.....	0	0	0
ES-5.....	3	3	5
ES-4.....	14	13	13
ES-3.....	3	4	4
ES-2.....	1	0	0
ES-1.....	1	2	0
Subtotal.....	22	22	22
Total - ES Salary.....	\$2,459,300	\$2,521,032	\$2,584,057
GS/GM-15.....	47	47	45
GS/GM-14.....	48	48	45
GS/GM-13.....	34	35	36
GS-12.....	41	41	41
GS-11.....	42	42	42
GS-10.....	1	1	1
GS-9.....	34	34	34
GS-8.....	28	28	28
GS-7.....	44	44	44
GS-6.....	29	29	29
GS-5.....	5	5	5
GS-4.....	11	11	11
GS-3.....	4	4	4
GS-2.....	1	1	1
GS-1.....	2	2	2
Subtotal.....	369	370	368

Grades established by Act of
July 1, 1944 (42 U.S.C. 207)

Assistant Surgeon General	1	1	1
Director Grade	24	24	24
Senior Grade	8	8	8
Full Grade	10	10	10
Senior Assistant Grade	4	4	4
Assistant Grade	0	0	0
Subtotal	47	47	47
Ungraded	128	142	144
Total permanent positions	407	418	418
Total positions, end of year	568	583	583
Total full-time equivalent (FTE) employment, end of year.....	572	590	590

Average ES level.....	4	4	4
Average ES salary.....	\$111,018	\$114,043	116,424
Average GS\GM grade.....	10.4	10.5	10.5
Average GS\GM salary.....	\$48,799	\$50,124	\$51,575

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Full-Time Equivalent Employment (FTE)

	<u>1995 Actual</u>	<u>1996 Estimate</u>	<u>1997 Estimate</u>
Office of the Director.....	61	61	61
Division of Diabetes, Endocrinology and Metabolic Diseases.....	18	19	19
Division of Digestive Diseases and Nutrition.....	15	15	15
Division of Kidney, Urologic and Hematologic Diseases.....	16	16	16
Division of Nutrition Research Coordination.....	4	4	4
Division of Extramural Activities.....	59	58	58
Division of Intramural Research.....	<u>399</u>	<u>417</u>	<u>417</u>
Total.....	572	590	590

Average GS/GM Grade

1992.....	10.5
1993.....	10.5
1994.....	11.0
1995.....	10.4
1996.....	10.5
1997.....	10.5

Note: Includes FTEs associated with HIV AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

TUESDAY, APRIL 23, 1996.

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

WITNESSES

DR. FRANCIS S. COLLINS, DIRECTOR, NCHGR

DR. HAROLD VARMUS, DIRECTOR, NIH

DR. ELKE JORDAN, DEPUTY DIRECTOR, NCHGR

JAMES C. VENNETTI, EXECUTIVE OFFICER

ERIN S. BURGESS, BUDGET OFFICER

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET,
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. MILLER [assuming chair]. Good afternoon. We will go ahead and begin. Chairman Porter is delayed at a speech he is giving and will be here shortly, so he asked if I would proceed with the program.

Doctor Collins, if you would like to proceed.

INTRODUCTION OF WITNESSES

Dr. COLLINS. Certainly. Thank you very much. I would like to introduce the people at the table. Accompanying me today are James C. Vennetti, my Executive Officer, Erin Burgess, the Budget Officer, Dr. Elke Jordan, the Deputy Director of the National Center for Human Genome Research, you know Doctor Harold Varmus, and Mr. Dennis Williams from the Department.

OPENING STATEMENT

This has been a truly exciting year for the National Center for Human Genome Research; a year which included a celebration of our fifth anniversary last October. I am grateful for the opportunity to appear before this committee today to describe current accomplishments of the Human Genome Project and also our plans for the coming year. Rather than simply listing off those scientific accomplishments, although I think you would find them gratifying, I have chosen instead to describe the Human Genome Project in the context of a family whose lives have been profoundly affected by this area of research, particularly in the past year.

I must say as a physician, I am reminded of the fact that the major reason for doing the Human Genome Project is to alleviate human suffering and for the medical benefits that will accrue. The Human Genome Project has many other justifying features—it is good basic science, it is good for the American economy, because it stimulates competitiveness in the international arena, and it will reduce health care costs. But as a physician, I keep coming back to the main reason we're doing the Human Genome Project. It is for families like the Marguses.

Brad and Vicki Margus with their four boys were recently featured on a program on ABC called "Turning Point" and in an issue of "People Magazine," could be said to have been a typical American family that had it all. A highly successful, energetic, attractive family. Brad runs a small company in Florida. About four years ago, Brad and Vicki began to notice that one of their sons, the second oldest, began to develop clumsiness. They took him to numerous physicians, but no one could quite figure out what was going on. They were told that maybe he was just having growing difficulties and he would grow out of this. But after another year they noticed that their third son was also developing the same symptoms. So now Brad and Vicki realized that their two boys, Jarrett and Quinn, were probably not both ill by coincidence and began going to a number of other doctors. They finally were given the correct diagnosis, which is Ataxia Telangiectasia. Lets call it AT for simplicity.

What do we know about this disease? It's a rare condition that affects about 1 in 40,000 individuals. The features are unfortunately deeply troubling and devastating to families in which this condition has occurred. Children are born looking entirely normal and then at about the age of two begin to develop clumsiness and coordination difficulties. They then become vulnerable to infections, they have a high risk of developing cancers of various sorts, especially leukemias and lymphomas, and their immune systems fail. Affected children are usually in a wheelchair by their teenage years, and they are usually dead in their twenties or early thirties. That is the future that this couple faced for two of their four sons.

This is a recessive condition, which means in order to be affected, as Jarrett and Quinn are, each parent has to carry an abnormal copy of the gene and by chance pass on that same abnormal copy to the same child. Carriers who have one normal copy and one abnormal copy are quite common; about 1 percent of the general population are carriers for AT. There's a good chance that somebody in this room is a carrier for AT. Yet, most people are completely unaware of it because they don't happen to have a child with somebody else who is also a carrier. This is an example of a situation where the study a rare disease turns out to have potentially significant consequences on a much larger scale.

AT—FINDING THE GENE

Obviously, for us to be able to get anywhere with understanding this disease, it was important to find the gene that's responsible for AT. That is a real needle in a haystack problem. We knew that it was out there somewhere and various groups had been working on this disease since about the early 1980s, but there are 100,000 genes and it was necessary to find the right one. This is where the tools of the Human Genome Project came into play. Studying families like the Marguses in which children had AT with a series of genetic markers, bits of DNA that you can trace through families, it was possible to map the disease gene to chromosome 11.

This was carried out using a process called linkage analysis. The panel of genetic markers which were used for that process and which have now been used to map hundreds of different diseases were, in fact, the first goal of the Human Genome Project. To

produce a set of these markers that would allow you to map any genetic disorder to its proper location. In 1990 we set what we thought was an ambitious goal that we felt we could achieve by the end of 1995. That goal was met instead a year and half early, in mid-1994. We now have a genetic map that's seven times better than expected at this point. Furthermore, within the last month, a genetic map has also been produced for the mouse which is about four times better than expectations and was also achieved a year ahead of schedule. So genetic maps are coming along beautifully. These contributed to getting the gene for AT narrowed down to a very small region of the long arm of chromosome 11.

Now, of course, you want to get from a region to the AT gene itself. For that you need physical maps, that is, collections or pieces of DNA that have been ordered and are known to overlap in defined ways. The second goal of the Human Genome Project is to get that kind of physical map. We thought it would take until the end of 1998 to have the physical map, but as of last December, a group of investigators at the Whitehead Institute at MIT published a physical map which is 94 percent complete. So we are happy to say that while we're not quite there, certainly within the next year or year and a half that physical mapping goal will also have been reached.

Then it is necessary to find the actual alteration in the gene to convince yourself that you have the right gene. Let me just give you an analogy to show about how big a DNA sequence may be to make up a gene. If you printed out all of the letters, the A, C, G, and T alphabet that makes up DNA, for the gene responsible for the disease that has afflicted the Margus family, the AT gene, it would fill a large book. Page after page of As, Cs, Gs, and Ts. That's a lot of information. However, it was possible using technology which has spun off of the Human Genome Project to come up with an alteration in the DNA of individuals like Garrett and Quinn and prove that this was the AT gene. That was accomplished by an international collaborative group led by Yosef Shiloh, an investigator in Tel Aviv, with collaboration from the Intramural Program of the National Center for Human Genome Research.

As a consequence of that discovery, it was possible for the Marguses to know that their youngest child will not be affected because he has not inherited two copies of this altered gene.

AT—UNDERSTANDING THE GENE

What does the AT gene do? Obviously, it is not just there to acquire a misspelling and cause a disease. It is there doing something important, but what? One of the first things to do is to take that sequence and see whether anything like it has ever been described before. This is done by doing a computer search of the world's database of sequences, which is maintained by the National Library of Medicine, called GenBank. That search was done and within minutes, seconds in fact, it was possible to say that there is another gene that somebody else has looked at that's very similar to this one. But it was found in yeast. Now, as it happens, yeast is a very useful model organism because it is a simple organism, but it still has a nucleus. Its genome that is all of its DNA, is much smaller than the human and, therefore, more accessible. And, in

fact, it was very useful to find out that there was a similarity there. That gene in the yeast turns out to be a gene which is also involved in the control of cell division just as we now believe the gene for AT is in humans. Now it has become possible to shift from studying a human disease which is difficult and requires great attention to human subjects, controls, and being sure that what you're doing is not toxic, to studying baker's yeast which has a very similar gene and learning ideas about how to treat this disease.

YEAST SEQUENCE COMPLETE

Now I can't resist telling you, although I'm jumping the gun slightly, that tomorrow morning we will announce in a press conference on the NIH campus that the yeast sequence, all 12.05 million base pairs of it, has been completed. This is a major milestone for genetics. Yeast will be the first organism, which we call a eukaryote which is the same class as humans, that has had all of its DNA figured out and which is now publicly available in a computer database. I think you will be reading about that in the newspapers in the next day or so, because having that sequence in hand is a real milestone and we're quite excited. Having that parallel between yeast and human DNA will allow us to make conclusions that we couldn't possibly do with the human alone.

For AT, having this gene sequenced means that we have passed through a bottleneck. We now have the opportunity to figure out how the gene works. This is being done in close collaboration with the National Institute of Neurological Disorders and Stroke and the National Cancer Institute, both of whom are very interested in this disease. There was a workshop in Philadelphia last weekend where more than fifty investigators came together to talk about AT. A few years ago, you probably couldn't have found three investigators who cared about AT. But now we've come through this bottleneck and it is clearly a very hot topic.

HUMAN GENOME PROJECT—STATUS OF GOALS

Now to summarize where we are with the goals of the Human Genome Project. It is fair to say that the genetic mapping goals have been achieved and, in fact, exceeded about a year and a half ago and the physical mapping goals are very close to being achieved. I would now like to turn to the DNA sequencing goals which are in many ways the most challenging. Three billion base pairs is the amount of DNA in the human genome. If you printed it out in books full of letters of average size and piled them on top of each other, they would be the height of the Washington Monument. Yet, we aim to have all of that sequence completed by the year 2005. Ambitious, indeed.

LARGE SCALE SEQUENCING OF HUMAN DNA

We announced two weeks ago the funding of six large-scale pilot projects to sequence human DNA which in aggregate will produce 100 million base pairs of sequence in the course of the next two years. That is about eight times greater than the total amount of human sequence that has been obtained by all of the world's laboratories working together. We will make sure that sequence will be

rapidly released. I am optimistic, based on the experience that we get through these projects, that we will be able to further scale up that effort and achieve the sequencing goal by the year 2005, or potentially even sooner. We will have to do everything possible to reduce the cost, which currently is about fifty cents a base pair in the best labs. We need to get that down to twenty cents or even ten cents.

We are already considering the consequences. What will it mean to have all of that sequence in hand, how will that change biology, what kind of scientists will we need to have ready to use that information and make the most of it. We have the opportunity to begin to tackle these questions with the yeast sequence that will be announced tomorrow. Last Friday we issued a request for applications for investigators to use that complete yeast sequence to figure out the biology of the organism.

AT—CONSEQUENCES—WHAT NOW

Let me close by going back to consequences for families and once again speak about the Marguses. I think you will agree that the identification of the Ataxia Telangiectasia gene catalyzed by the Human Genome Project has provided a remarkable step forward for this disease, although the therapeutic benefits for Jarrett and Quinn lie largely in the future. Meanwhile, what about Brad and Vicki? It turns out that carriers for AT, which they are, appear to have an increased risk of cancer themselves, perhaps as much as three-to fivefold increased risk for things like lung cancer, stomach cancer, breast cancer or melanoma. Are they at risk of losing their health insurance? Are they at risk of losing their jobs because of a concern about their future health risk? That seems unusually cruel. Here is a couple who are already facing serious illness in their children, and now for themselves they may also be discriminated against because of genetics. The American public is concerned about this. A recent Harris Poll documents 82 percent of the people they asked expressing concerns about genetic discrimination particularly in insurance and employment.

[CLERK'S NOTE.—Subsequent to the hearing, NCHGR corrected this figure to "86 percent" for the record.]

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS PROGRAM

The ELSI Program of the Human Genome Project, the Ethical, Legal, and Social Implications Program to which we devote 5 percent of our budget, is very much focused on these issues of genetic discrimination and has been a successful experiment in the course of the first five years. The ELSI Program is partly scholarship, we've now funded 126 grants on these issues, and it is partly an analysis of the issues and a proposal of policy options. The ELSI Working Group is largely charged with the latter. You may have seen last Sunday night on "60 Minutes" a story about health insurance discrimination. The story focused heavily on advances in the Human Genome Project, and the growing consensus on the need to do something to prevent discrimination.

DISCRIMINATION BASED ON GENETICS

I am happy to say that things are happening. In the area of insurance discrimination, not only have 12 States put together legislation and passed it to, at some level, prevent the use of genetic information to deny people coverage, but here in the United States Congress, both in the House and the Senate, several bills have been introduced. This very day in the Senate the Kassebaum-Kennedy bill is being voted on which specifically mentions genetic information as one of the things which should not be used to deny coverage to Americans. Many of us are quite pleased to see that happening. Protections against employment discrimination, although not perfect, have also been instituted by the Equal Employment Opportunity Commission in the past year and a medical records privacy bill, the Bennett bill, is also under serious consideration in the Senate.

GENETIC TESTS IN CLINICAL PRACTICE

We are also looking at the question of the integration of genetic tests into clinical practice. When is it time for a test to leave research and find its way into the clinic? There has been much discussion about this, particularly for breast cancer. A Task Force on Genetic Testing, which is a subgroup of the ELSI Working Group, has been meeting for the past year and as recently as one month ago produced a series of draft principles, 41 of them, for which public comment is now being sought.

ISSUES IN RESEARCH AND EDUCATION

In the area of research, we're very concerned about human subjects issues in genetic research. Again, good scholarship has been done in that regard and standards have been proposed. Finally, education of health professionals is a critical issue. If we're going to move genetics out of research into the clinic, we need physicians and nurses that are ready to take this on. I met this morning with the American Medical Association and the American Nurses Association to talk about these issues and got a very warm reception. I think everybody recognizes this is important.

So I would say the ELSI effort has been a successful one. We have a cadre of experts, we have defined the issues, there is a deep and significant body of scholarship, there's serious analysis of policy options, and now in some instances we need legislative interventions.

AT—HGP OFFERS HOPE FOR THE FUTURE

To conclude, some have called the Human Genome Project the most significant organized scientific undertaking that humankind has ever mounted. Obviously, I would agree. I believe it holds within it the seeds of hope and deliverance for families like the Marguses, although that eventual realization is some time off. In effect, that applies to all of us. All families are in the situation where members of that family are at risk for something. We all carry around alterations in our DNA that place us at some risk.

The final two sentences in the "People Magazine" story about the Marguses read: "Finding the gene isn't a cure, of course. But if you

ask Brad Margus, he would say that now there's hope." Hope is an interesting word. There's a quote I'm very fond of from Peter Levi: "Hope in every sphere of life is a privilege that attaches to action. No action, no hope." The Human Genome Project and the whole NIH is about action.

Mr. Chairman, the budget request for the National Center for Human Genome Research for fiscal year 1997 is \$177,788,000. I will be very happy to answer any questions you have.

[The prepared statement and biography of Dr. Francis Collins follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Center for Human Genome Research

Mr. Chairman, the National Center for Human Genome Research began this fiscal year with a celebration of the fifth anniversary of the Human Genome Project. With virtually all of the goals for those first five years already met, we celebrated our anniversary with great excitement. The genetic mapping goal for the human was met in 1994, more than a year ahead of schedule. Just last month, researchers published final genetic maps of both the human and the mouse. These combined accomplishments complete the genetic mapping phase of the Human Genome Project.

Scientists are also close to completing the physical map of human DNA. This past year, researchers at the NCHGR-supported genome center in Cambridge, Massachusetts, published a map that represents 94 percent of the human genome in identifiable, cloned pieces of DNA. Through that effort and those of other NCHGR-supported laboratories, we will finish the physical map in 1997, and probably even sooner. Already, the current physical map provides researchers with a starting point for sequencing human DNA.

As a result of those accomplishments, we have seen an enormous increase in the number and kind of disease genes being discovered. Not only are the so-called single-gene disorders giving up their secrets, but we are beginning to see the same discoveries for complex disorders, such as diabetes, prostate cancer, Alzheimer's disease, and breast cancer--disorders that are quite common in this country. In contrast to just a few years ago, genome project technologies are now commonplace in biomedical research laboratories of every size and in almost every corner of the globe. Scientists access genome project data in NCHGR-supported, public databases some 150,000 times per week.

With the genetic-mapping phase of the Human Genome Project concluded, and the physical-mapping phase coming to a close, we now face the project's most challenging goal: to determine the sequence of all of the nucleotide bases that make up human DNA. The thread of DNA found in a single cell, when unraveled, stretches to about six feet long. Encoded within that six-foot strand is the language of life. It is spelled out in 3 billion letters, combinations of A, T, C, and G, which represent the chemical names of the DNA building blocks. If you were to print out all the information in the human genome, letter by letter, it would fill a stack of books about as tall as the Washington Monument.

That information contains what our bodies need to know to function properly, how a baby develops, how we age, how humans are biologically different from animals, and how we are the same. DNA also contains clues about diagnosing and treating diseases that arise from misspellings in the DNA language. Indeed, such misspellings contribute to almost every human disease.

From the beginning, the Human Genome Project's sequencing research focused on improving speed and lowering cost. This work focused on the DNA of laboratory organisms until technologies

were efficient enough to take on the large and complex human genome. Progress in these scale-up projects has been remarkable. Several laboratories have now obtained at least 1 million base pairs of DNA sequence at a cost of about \$1 per base pair; a few can do it for about 50 cents per base pair. This represents a dramatic reduction in the cost of DNA sequencing from \$5-\$10 per base pair when the Human Genome Project began. New strategies for system management, integration and miniaturization of components, and increased automation are likely to produce even further reductions in cost.

A collaborative project between NCHGR-supported researchers in St. Louis and their colleagues in Cambridge, England, for example, has amassed 28 million bases of DNA from the genome of the roundworm, *Caenorhabditis elegans*. This represents the largest amount of genomic DNA catalogued for a single organism. The St. Louis-Cambridge group can now produce 15 million base pairs of DNA sequence per year, and that rate is increasing. These investigators expect to complete the sequence of the roundworm genome, which contains 100 million base pairs, by the end of 1998. Another international team sequencing the yeast genome will complete that project imminently. The finished sequence of yeast, all 15 million base pairs, will represent the largest complete genome sequenced to date. And it provides an enormous amount of useful data in deciphering the function of genes in the yeast, many of which are strikingly similar to human genes in both structure and function.

Success with sequencing model organism DNA has encouraged us to begin pilot studies to sequence the large and complex human genome. Last year, NCHGR issued a request for applications asking investigators to propose large-scale pilot projects on sequencing the human genome; these proposals have been reviewed and approved by the NCHGR advisory council, and several awards will be issued in the very near future.

These pilot projects to sequence human DNA officially mark the beginning of the final stage of the Human Genome Project. This is the most complicated undertaking in biology, and indeed the beginning of a new way of thinking about biology and medicine. With the complete DNA sequence of the human in hand, what kinds of questions will scientists be able to ask, and more importantly, what answers will they get?

To glimpse at the future of biology, NCHGR sponsored a symposium, called *Visions of Sequence-Based Biology* as part of our fifth-anniversary celebration. Some of biology's best thinkers gathered to offer a vision of a new era of large-scale biological analysis. In this new era, scientists will study cells, not by breaking them down into thousands of individual pathways, as science has generally done, but as intact, functioning biological networks. This will allow tracking of expression patterns of thousands of genes at once, applying the information encoded in DNA sequence to explore the physical properties of proteins--the chemical workhorses in the cell--and ultimately, probing more powerfully the complex biocircuity of cells, tissues, organs, and perhaps, entire organisms. We will ask not just how a single gene works, but how hundreds, perhaps thousands, of genes work together to make a tissue or an organ function; how thousands of genes work together to fashion a functioning body out of a single, fertilized egg cell; how information contained in a linear strand of DNA is translated into three-dimensions to make proteins that carry out all of the miraculous tasks a body performs in a day or a lifetime. We will

understand more clearly not only our own genetic uniqueness, but also our relatedness to others both near and far from our place of origin.

Answering the questions of 21st-century biology will require us to take several snapshots of genome function in different individuals at different times. The information will be most useful if it can be manipulated and compared quickly and cheaply. Comparing differences in large regions of the genome—several million bases or more—among many individuals will yield an enormous amount of information about the mechanism of inheritance, such as disease susceptibility, response to certain environmental influences, and even evolution. So, even as some researchers begin production sequencing of the human genome, NCHGR will continue to support development of new methods for sequencing that will meet the demands for even lower-cost sequencing and comparison of very large genome regions.

In NCHGR's Division of Intramural Research (DIR), scientists are already using large-scale approaches to study human genetic diseases. DIR investigators utilize cutting-edge genome science to develop streamlined techniques to rapidly isolate and analyze disease-linked genes, generate improved methods to diagnose inherited and acquired genetic disease, and investigate treatment strategies.

Identifying the several genes that play a role in predisposing individuals to more common diseases is a particularly challenging task because it requires the analysis of large amounts of genetic information from large numbers of individuals. In collaboration with industry, DIR investigators are experimenting with high-throughput methods to scan the complete genetic make up of thousands of individuals to sort out the contributions of multiple genes to complex disorders. Using these approaches, they are on the trail of the genetic basis of adult-onset diabetes (there are 6.57 million new cases of diabetes among Americans each year) and of prostate cancer (there are 240,000 new cases of prostate cancer among Americans each year). In another project, DIR researchers are using combinations of fluorescent dyes to develop new methods for analyzing chromosomal changes in whole genomes. The new approach makes it much easier to identify disease-linked changes in chromosomes, which may not be visible using standard microscope techniques. Using this technique, for example, DIR scientists have identified an important new chromosomal abnormality associated with the transition to invasive cervical cancer. Other tumors are being studied in a similar manner, including astrocytomas, breast cancers, colorectal cancers, and lymphomas.

In the larger context, we have already begun to see that the biology of human beings is intertwined with our social networks. Are these institutions keeping pace with the explosion of knowledge we are gaining about ourselves? Are they allowing us to reap the maximum benefit from this new knowledge?

The NCHGR Ethical, Legal, and Social Implications (ELSI) program has focused on several high-priority areas raised by the most immediate potential applications of genome research: privacy and fair use of genetic information; responsible clinical integration of new genetic technologies; ethical issues surrounding the conduct of genetics research; and, professional and public education about these issues.

Two key initiatives are underway to address crucial questions surrounding genetic testing, especially for cancer susceptibility. NCHGR and several other NIH Institutes are co-sponsoring a Cancer Genetics Studies Consortium, focusing on the psychological and social impact of cancer testing on individuals and their family members. Recommendations for approaches to genetic testing and counseling for cancer risk are being developed. The studies are well underway, and the investigators have developed draft recommendations for how to counsel patients and families who carry mutations in the major gene for heritable breast cancer, BRCA1.

A second group, the Task Force on Genetic Testing (TFGT), was established by the ELSI Working Group to examine the development and delivery of safe and effective genetic tests and the quality of the laboratories providing the tests. Task Force membership includes representatives from the biotechnology industry, the professional medical and genetics societies, the insurance industry, consumers, and federal agencies. In light of the rapid pace of disease-gene discovery and genetic test development, the findings of the TFGT will be crucial to the development of sound policies and practices for the introduction of new genetic tests. The group has now issued draft principles and expects to complete its work in early 1997.

As our knowledge grows about the genetic basis of disease, so too does the potential for discrimination and stigmatization based on the information contained in our genes. Of particular concern is the fear of losing jobs or health insurance because of a genetic predisposition to a particular disease. A woman who tests positive for BRCA1 has an 85 percent likelihood of developing breast cancer. Fighting that risk with intensive surveillance or surgery, without health insurance, would result in economic ruin and probable tragedy.

Nevertheless, there are no Federal laws now in place to prevent health insurance companies from using genetic information to deny coverage. Several states, including California, Florida, Ohio, and Wisconsin, have passed legislation aimed at protecting individuals from being denied health insurance based on their genetic status. However, state laws do not provide protection for the many Americans who obtain their health insurance coverage through employer-based plans, because the Federal Employee Retirement Security Act (ERISA) exempts self-funded plans from state oversight.

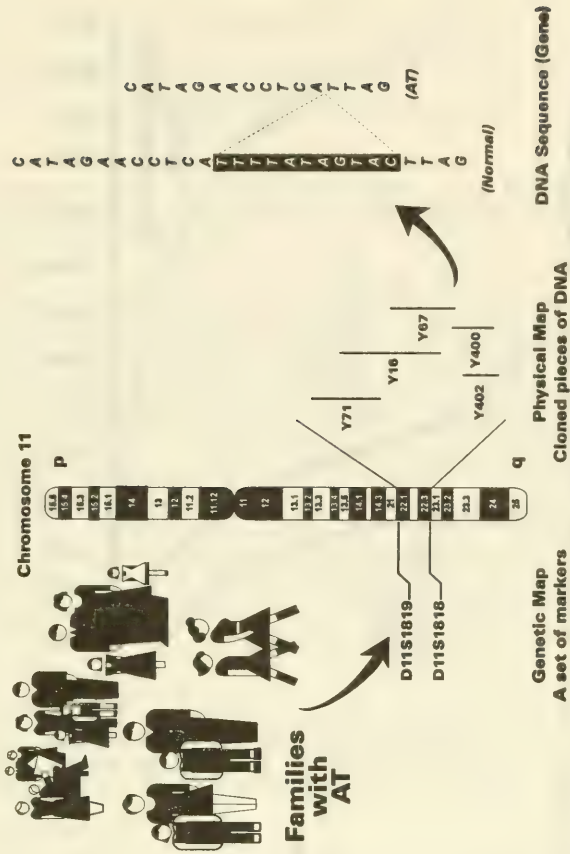
The ELSI Working Group has long been involved in discussions about the fair use of genetic information, particularly as it relates to health insurance. In 1993, the ELSI Working Group's Task Force on Genetic Information and Insurance concluded that, "Information about past, present, or future health status, including genetic information, should not be used to deny health insurance coverage." Building on their shared concerns, the ELSI Working Group and the National Action Plan on Breast Cancer (NAPBC), a public-private partnership established to address the research, education, and policy issues in breast cancer, co-sponsored a workshop last July to address the issue of genetic discrimination and health insurance. Consumers, researchers, federal and state government representatives, and insurance industry representatives came together with the members of these two groups to participate in the one-day session. The ELSI Working Group and the NAPBC developed and published recommendations for state and federal policy makers to protect against genetic discrimination.

The knowledge explosion in human genetics is already changing biomedical research and the practice of medicine. To make the best use of the opportunities this brings, health care providers must have the knowledge, skills, and resources to apply new knowledge and technologies to the diagnosis, prevention, and treatment of disease. In addition, an informed provider-patient relationship is mostly likely to result in the best health care.

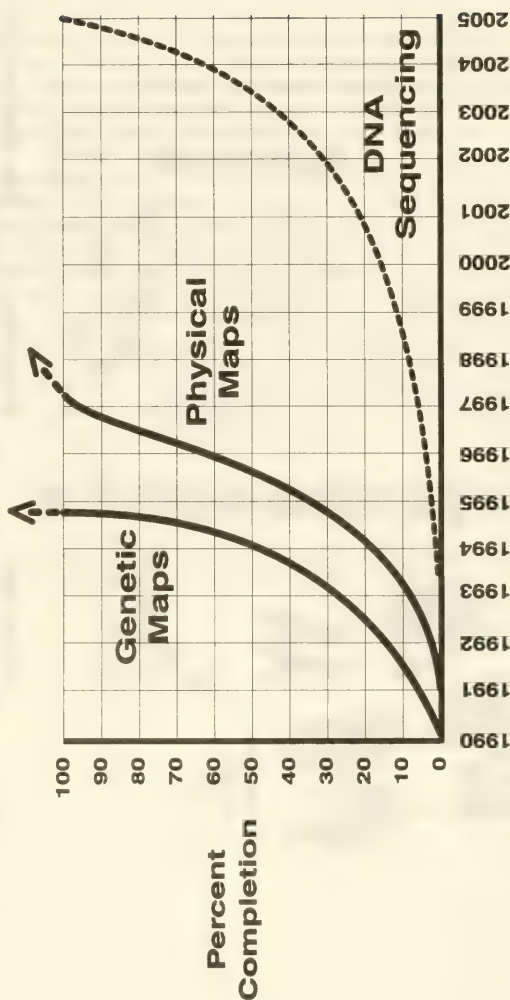
The ELSI program has funded a number of educational efforts designed to increase the level of genetics knowledge among health care professionals and the public, including surveys to assess health professional knowledge in genetics and the development of genetics curricula. In 1995, NCHGR held a meeting of health professionals and education experts to define education priorities for the ELSI grant program. These experts concluded that while both public and professional education are important, professional education is of highest priority since health professionals will be the principal source of patient information. Health professionals will provide information about the appropriateness of genetic testing, be responsible for the interpretation of genetic tests, and incorporate test results into continued patient care. As a result, a new grant solicitation document explicitly states that health professional education is a high priority and encourages investigators to submit applications for projects that will improve professional understanding of genetics and genome technology.

In the Division of Intramural Research, education programs are under development or in place for genetic counselors, nurses, and M.D. and Ph.D. fellows in medical genetics.

Mr. Chairman, the budget request for the National Center for Human Genome Research for fiscal year 1997 is \$177,788,000. I will be happy to answer any questions.



Human Genome Project Progress



FRANCIS S. COLLINS, M.D., PH.D

Director, National Center for Human Genome Research

April 14, 1950. Staunton, Virginia

Education:

University of Virginia, 1970 - B.S. (with Highest Honors); Yale University, 1972 - M.S.; Yale University, 1974 - Ph.D.; University of North Carolina School of Medicine, 1977 - M.D. (with Honors)

Professional History:

1976-1977, Fellow in Genetics and Biochemistry, University of North Carolina School of Medicine, Chapel Hill, North Carolina. 1977-1978, Intern in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1978-1980, Assistant Resident in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1980-1981, Chief Resident in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1981-1984, Fellow in Human Genetics and Pediatrics, Yale University School of Medicine, New Haven, Connecticut. 1984-1988, Assistant Professor of Internal Medicine and Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan. 1987-1988, Assistant Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1987-1991, Chief, Division of Medical Genetics, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan. 1988-1991, Associate Professor of Internal Medicine and Human Genetics, University of Michigan School of Medicine, Ann Arbor, Michigan. 1988-1991, Associate Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1991-1993, Professor of Internal Medicine and Human Genetics, University of Michigan School of Medicine, Ann Arbor, Michigan. 1991-1993, Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1993 to present, Director, National Center for Human Genome Research, NIH, Bethesda, Maryland.

Board Certification:

Board of Medical Examiners, State of North Carolina, 1977
American Board of Internal Medicine, 1980
Board of Medical Examiners, State of Connecticut, 1981
American Board of Medical Genetics, 1984
Board of Medical Examiners, State of Michigan, 1984

Professional Organizations:

American Association for the Advancement of Science; American Society of Human Genetics, Human Genome Committee, Ad Hoc Committee on Cystic Fibrosis Screening, Board of Directors; American Scientific Affiliation; American Federation for Clinical Research; American Society for Microbiology; American Society of Hematology; American Society for Clinical Investigation; Human Genome Organization (HUGO), Executive Council; Institute of Medicine; National Academy of Sciences.

Editorial Boards.

Associate Editor, The American Journal of Human Genetics, 1986-1989. Currently: Associate Editor, Genomics; Associate Editor, Technique; Associate Editor, Genes, Chromosomes, and Cancer; Associate Editor, Somatic Cell and Molecular Genetics; Associate Editor, Human Molecular Genetics; Human Mutation.

Awards and Honors:

Dean's Prize for Academic Excellence, 1970; National Science Foundation Graduate Fellowship, 1970-1973; Morehead Foundation Fellow, 1973-1977; Alumni Loyalty Merit Award, 1974; Deborah C. Leary Research Award, 1975; First Prize, Student Research Day, 1975; Riggins Scholarship, 1975; Heusner Pupil Award, 1976; W. Reece Berryhill Scholarship, 1976; Medical Faculty Award, 1976; Isaac Hall Manning Award, 1977; Alpha Omega Alpha, elected Junior year, President of UNC chapter, 1976-1977; Intern of the Year Award, 1978; Henry C. Fordham Senior Resident Award, 1980; Charles E. Culpepper Foundation Fellow, 1983-1984; Cooley's Anemia Foundation Fellow, 1983-1984; Anthony Renda Research Grant, 1984-1985; Hartford Foundation Fellowship, 1985-1987; Jerome Conn Research Award, 1986; Paul di Sant'Agnese Award of the Cystic Fibrosis Foundation, 1989; Honorary Doctor of Science, Emory University, 1990; James A. Shannon Lecturer, Massachusetts General Hospital, 1990; Elizabeth Crosby Teaching Award, 1990; Cairdner Foundation International Award, 1990; Von Recklinghausen Award of the National Neurofibromatosis Foundation, 1990; Michiganian of the Year, The Detroit News, 1990; Lynen Medal of the Miami Bio/Technology Symposium, 1991; Young Investigator Award of the American Federation for Clinical Research, 1991; Honorary Doctor of Humane Letters, Mary Baldwin College, 1991; Doris Tulcin Award for Cystic Fibrosis Research, 1991; Elected to Institute of Medicine, 1991; Distinguished Faculty Achievement Award, University of Michigan, 1991; National Medical Research Award, National Health Council, 1991; Dickson Prize, University of Pittsburgh, 1991; Association of American Physicians, 1992; Honorary Doctor of Science, Yale University, 1992; Honorary Degree of Doctor of Science, The Mount Sinai Medical Center, 1993; Jack Saint Clair Kilby Award, 1993; Kaiser Permanente Award for Excellence in Teaching, University of Michigan, 1993; National Medical Research Award (as member of Huntington's Disease Collaborative Research Group), National Health Council, 1993; Sarstedt Prize for Scientific Research, Dresden, Germany, 1993; CIBA-Geigy/Drew Award in Biomedical Research, Drew University, 1993; John M. Nokes Lecture, University of Virginia, 1994; National Organization for Rare Disorders Scientific Leadership Award, 1994; Honorary Doctor of Science, University of North Carolina-Chapel Hill, 1994; Nelson Award, University of California-Davis, 1994; Lovelace Institute Award for Excellence in Environmental Research, 1994; George D. Aiken Lecture, University of Vermont, 1994; American Academy of Achievement Golden Plate Award, 1994; Steven C. Beering Award for Outstanding Achievement in Biomedical Science, Indiana University, 1994; The Baxter Award for Distinguished Research in Biomedical Sciences, Association of American Medical Colleges, 1994; Willis M. Tate Distinguished Lecture, Southern Methodist University, Dallas, Texas, 1994; Jean-Pierre Lecocq Prize, Transgene, S.A., Strausbourg, France, 1994; Lila Gruber Cancer Research Award, American Academy of Dermatology, 1995; Jeffrey Modell Foundation Lifetime Achievement Award, The Jeffrey Model Foundation, Inc., 1995; Neuhauser Lecture, The Society for Pediatric Radiology, 1995; Lee Farr Lecture, Yale University, 1995; American Association for Clinical Chemistry National Lectureship Award, 1995; Hatfield Lecture, Oregon Health Sciences University, 1995; Susan G. Komen Breast Cancer Foundation National Award for Scientific Distinction, 1995; John Hickam Lecture, Central Society for Clinical Research, 1995.

Mr. PORTER [assuming chair]. Doctor Collins, let me also welcome you here today. I was sorry I was busy making some remarks that carried over a little bit. I thank my colleague from Florida, Mr. Miller, for opening our hearing today.

My first question is, are you still riding your motorcycle?

Dr. COLLINS. Absolutely. Especially on a day like this.

COST OF SEQUENCING

Mr. PORTER. Good. You've got things in perspective. When the partial physical map was released, you were quoted in the New York Times as saying that the next phase sequencing is expected to be "very expensive." What does this mean for your center's budget in the outyears?

Dr. COLLINS. The partial physical map you are referring to was completed last December and we were quite excited about it because it does provide the raw materials needed to move into the sequencing phase in a big way. That was one of the things we were waiting for. The other was for the technology for sequencing to get reasonably priced enough that it was imaginable to launch into this phase of the Human Genome Project. That has also happened although the price needs to drop still further to get the whole thing done.

Yes, it is very expensive. Well, 3 billion base pairs at 50 cents a base, which is the current best price that the most organized centers have been able to manage, that's still \$1.5 billion. We don't have that much money in the current budget for the National Center for Human Genome Research and the DOE's genome program. So we have to reduce that cost further.

Over the next two years in these just initiated pilot projects, we're going to find out just how hard that is. At least one of the six centers thinks they can get the price down to about 25 cents at the end of those two years. If we can get it to 20 cents, then we can probably just squeak through. But I'm not going to be satisfied with that, Mr. Chairman. I think we should aim for 10 cents or less, because if we are able to do that, then we can finish earlier, and possibly expand even further the number of model organisms. I would like, for instance, to have the chance to sequence all of the mouse DNA. But we can't do that if we don't get the price down further.

LARGE-SCALE SEQUENCING OF HUMAN DNA

Mr. PORTER. Earlier this month you announced a \$60 million pilot study of large-scale sequencing. What benchmarks have you set for the pilot to determine whether it is feasible to continue investing in large-scale sequencing?

Dr. COLLINS. This is actually going to be a very interesting experience. We have pretty much told these six centers who we are funding what's going to be expected of them. We are going to review them within two years, that's a much shorter time period than normal, but this is a large investment so we have to keep close tabs on what's happening. In a way, reviewing these projects is easier than some other parts of science because you have very clear indications of success. How much sequence have they deposited in a public database, what did it cost, how accurate was it, and

did they deposit it in a public database in a timely fashion? That's how we're going to evaluate. Those are our milestones.

Those centers are going to produce varying amounts of sequencing depending on their funding. In aggregate, we expect to have 100 million base pairs and we expect the accuracy to be 99.99 percent, or only 1 mistake in every 10,000 base pairs. That seems to be an achievable goal. We expect there to be no more than 1 percent of the sequence that's in gaps and for that 1 percent we expect to know how big the gaps are and to have an easy way to close them later for people who are interested. Those are the goals. They are very explicit. The six centers will be evaluated on the basis of that. The centers that have achieved those goals will expand their operations in the third year. The centers that have not will be phased out.

INTERNATIONAL COLLABORATION

Mr. PORTER. In Britain, the Wellcome Trust has committed \$75 million over seven years to high speed sequencing. Has the Wellcome Trust funding decreased the level of effort that will be required by your Center?

Dr. COLLINS. In some ways, yes. The Human Genome Project is an international effort and that's as it should be. The genome belongs to all of humankind. It is appropriate therefore that all countries that have the wherewithal ought to be participating in this. The Wellcome Trust is very committed to seeing a significant effort carried out in England at the Sanger Center in Cambridge under the direction of Doctor John Sulston. There is a long-standing and very productive collaboration between Doctor Sulston in Cambridge and Doctor Robert Waterston at Washington University in St. Louis. This is basically a continuation of a partnership which they have been carrying out very successfully on the roundworm *C. elegans* and are now expanding to obtain the human sequence as well. I believe that contribution will be well done.

There obviously needs to be close coordination so that we don't end up sequencing the same region of the same chromosome more than once; there's enough to do without doing it twice. At a recent meeting of all the international groups that are going to be contributing to sequencing, a system was set up where each group will let it be known on a public web page which part of the genome they are working on and which part they are about to start on. That will allow much less opportunity for duplication of effort. So I am quite gratified in fact by what the Wellcome Trust is doing.

Mr. PORTER. Thank you, Doctor Collins. Ms. Lowey.

GENE FOR BREAST CANCER

Ms. LOWEY. Thank you, Mr. Chairman. Thank you, Doctor Collins, for appearing before us today. I first of course want to congratulate you and the Center for Human Genome Research for the breathtaking work, path-breaking work in mapping the human genome, and I share in your hope that by understanding the genetic basis of disease we can eventually eliminate a great deal of the human suffering associated with diabetes, prostate cancer, Alzheimer's, and breast cancer, just to name a few.

I would like to ask you some questions concerning the breast cancer gene BRCA1 which has been discovered in the Jewish population. As I understand it, it was discovered in 1 percent of the sample of Jews of Ashkenazi descent. And also as I understand it, if the study found that the gene was present in woman with a history of breast cancer in her family, then she had an 85 percent chance of contracting breast cancer.

Dr. COLLINS. That's right.

Ms. LOWEY. Before I get to the lookback study, perhaps you can clarify a few points for me. One, what was the size of that study? In making the determination that 85 percent have the chance of contracting breast cancer, was there any determination of whether it would be contracted in five years, ten years, fifty years, sixty years? Thirdly, what was the age of the group that was studied, because I think this is very relevant. One of my real concerns, and I we'll get to that later, is the commercialization of this test before we're ready to really deal with it, and the incidence of women prophylactically having their breasts removed because there is such a fear of this illness. But perhaps you can answer these first questions first.

Dr. COLLINS. Certainly. I share those concerns, Ms. Lowey. I appreciate the question. How do we know these numbers? The 85 percent risk of breast cancer in a woman who has a misspelling, a mutation in the BRCA1 gene, is based upon an analysis of 214 families. Those are not all families with the Jewish mutation; those are families that have BRCA1 misspellings of all sorts. So far, it has not been possible to discern if there are great differences in risk between those families, depending on the specific misspelling, but one worries that there might be. That 85 percent number is not specifically derived just from Jewish women who have this one very particular two letter deletion that you referred to. It is, in fact, aggregating together families of many sorts. Probably only about 10 percent of those were Jewish families. So that is a very soft number. The 85 percent risk estimate could be too high, could be too low; we don't know yet.

Ms. LOWEY. Wait a minute. If I could just follow up on that. You are saying that of the 214 families only 10 percent were Jewish but the determination has been that 85 percent have a chance of contracting breast cancer. So how many families were there then in the study?

Dr. COLLINS. About 20 of those 200 families were Ashkenazi Jewish. Now looking at those 20 separately from the rest, the risk of breast cancer does come out about the same. It looks like it's about 80 to 90 percent. There aren't enough subjects to be certain of the precision of that number but it's clearly very high.

There is a problem, however, with generalizing from that statement. What about a woman who has not been identified, by being part of one of those large families, but who comes in and has her blood sampled and turns out to have this Jewish breast cancer mutation? Is her risk 85 percent? We're not entirely sure of that. You could say that the way we've collected the data so far has been biased. We specifically have been looking for families that had a lot of breast and ovarian cancer, that's how they got into the study. It could, therefore, be that the true risk of breast cancer in an un-

biased sample will be somewhat lower. There are studies underway, and you referred to one of them, to try to get us better answers to that question before we are in the position of trying to counsel women who are found to have this alteration about what it means.

Ms. LOWEY. Can you just give me the age group of those who were in that study.

Dr. COLLINS. It was all ages. One can construct a curve of the risk of breast cancer as a function of how old that individual is. And for those 214 families, again, the risk is about 50 percent by age 50, and it is 85 percent life-long. This is early onset disease because age 50 is pretty young for breast cancer, but that risk continues even into an older age group.

VERIFYING THE PREVIOUS STUDY

Ms. LOWEY. I know that NCI is currently conducting a lookback study in the D.C. metropolitan area to confirm this initial finding. If the findings of this initial study are confirmed, can you comment on how common this particular gene would be within the Ashkenazi Jewish population relative to other genes found in ethnic groups. For example, would it be more common than Tay-Sachs disease which is also prevalent in the Jewish community? I'm trying to understand within this small sample how serious this is relative to your findings of a similar kind of genes related to other diseases.

Dr. COLLINS. I understand. The National Center for Human Genome Research is collaborating with the NCI on the lookback study. I met yesterday with the group that is doing this, and they have just about completed ascertaining 5,000 individuals. The goal here is to try to learn whether that 85 percent number is right or not by doing a study which is not biased in the same way. We hope to know something concrete by September.

So far, the likelihood of having this particular two letter deletion in the Jewish population appears to be about 1 percent—the original study found 8 individuals out of 858. That's probably about the right number. That is a very common genetic alteration. You asked about Tay-Sachs as a comparison. It depends on how you ask the question. Tay-Sachs is a recessive disease. In order for a child to be affected, both parents have to be carriers and then the child has to inherit the abnormal copy from each of them, as with the AT gene that I was talking about. Tay-Sachs disease is actually fairly uncommon but the carrier state in the Jewish population is fairly common, 5 or 6 percent. [CLERK'S NOTE.—Subsequent to the hearing, NCHGR corrected these figures to "3 or 4 percent" for the record.] So there are more Tay-Sachs carriers in the Jewish population than there are individuals with a BRCA1 mutation. But the consequences of being a Tay-Sachs carrier are very limited unless you happen to have a child with another carrier, whereas the consequences of having a BRCA1 mutation if you're a woman are significant. This particular BRCA1 situation is about the most common serious genetic disorder yet described in any ethnic group. It is quite surprisingly frequent.

Ms. LOWEY. Thank you, Doctor Collins.

Mr. PORTER. Thank you, Ms. Lowey. We will have a second round. Mr. Miller.

MEDICAL BENEFITS OF GENOME RESEARCH

Mr. MILLER. Dr. Collins, you mentioned the story about the Marguses and genetic diseases. An area that I'm always very interested in is the area of hemophilia, which is a genetic disease, of course. You talk about how we're making progress at the basic science level, but where do the applications come along? Besides the potential diagnosis, which is helpful, of course, and necessary, where do you see the medical benefits for the treatment and cure and prevention of some of these things and how far off are we from seeing those type of realizations?

Dr. COLLINS. I think that's the question that everybody wants the answer to. I guess at some level I want the answer to it too. But I will give it a shot. The consequences of gene discovery are of several types. Almost immediately after you identify a gene, whether for hemophilia or for AT, you have better diagnostic abilities to determine whether somebody has the disease or is going to get it or is at risk of having a child with it. Those come along very quickly. But you're asking about the therapeutic advances. When will we have a cure for hemophilia? When will we have a cure for AT? Those are much harder to predict. They will come about, I am confident of that, but the timing is something which one can't necessarily engineer.

For some diseases, and I think hemophilia is a good candidate, the therapeutic advance may come about through gene therapy. In that circumstance, a gene is not producing the protein that it is supposed to. So scientists are trying to engineer that gene into a vector, deliver it to the appropriate tissue and get it to produce that protein. As you know, gene therapy had a bit of an up and down course in the past year and I think we've had a very reasonable mid-course correction through the panel that Doctor Varmus put together to review the field. The panel concluded that we need lots more good solid basic science before this still very new field can be said to have matured to the level that one would like. Gene therapy is still sort of a baby in the crib. It is not fair to criticize a baby in the crib too severely if it hasn't gotten up and walked. But you need to be sure that you're nurturing it along so that it will get up and walk. That panel also said that gene therapy has extraordinary potential. I think we all agree with that but you have to develop that potential. So when will gene therapy for hemophilia be here? I can't tell you exactly. There are experiments in the Intramural Program of NCHGR targeted towards hemophilia but they are probably several years away from a realistic test of whether this is going to be of benefit in human patients. Much work still needs to be done in animal models.

The gene therapy approach will not always be appropriate. Disorders, that affect the brain or where the problem is not that you're missing something but that you're producing a toxic protein, those may be more appropriately dealt with by a drug therapy. The problem is that most drug therapies we use right now are rather empiric; they were not arrived at by an understanding of what is precisely wrong in the cell, but rather by just trying things. We have

got to do better than that. The promise of all these gene discoveries is that we will do better than that because we'll understand the really intricate workings of the cell and that will give us the ability to design small molecules to interfere with the disease processes that are currently frustrating us. But knowing the timetable is really impossible. If anybody promises you that they're going to tell you how long it's going to be, they're not being straight with you. None of us can really say that. Obviously the answer is more research and better research more thoughtfulness in to how to do that research and taking advantage of opportunities that come along. But this is a golden era; things are happening very fast. People will probably look back on this time and say, gee, how come they didn't realize that they were right around the corner from some big breakthrough. You don't know a breakthrough until you hit it.

PATENTING AND AVAILABILITY OF INFORMATION

Mr. MILLER. This is obviously one of the exciting things that Dr. Varmus gets to talk about, some of the other areas might be a little more dull I think at the National Institute. So it is exciting to be a part of this particular program. Let me ask you a question in continuation. The commercialization and spin-offs of some of the results, how is that going to happen? And the competition between drug companies and the patenting of issues. This is part of that ethics issue, too, and the fact that people may protect certain information and sharing information. Discuss that for a minute if you would.

Dr. COLLINS. Yes, it's a very complicated issue. I think we always said that the Human Genome Project would only realize its full potential if it resulted in a great deal of interest in the private sector to take what's being produced and turn it into products, into therapies. Academia is not necessarily the place to get that over the finish line. So I am delighted to see that happening. A recent tally suggests that more than \$800 million has been invested by pharmaceutical companies in genome research in the course of the last three years—very clear evidence that the pharmaceutical companies are interested in this and are spending their own money on it. You can't find a pharmaceutical company now that doesn't have a genome division. They perceive that the strategy where gene discoveries lead you to new drugs is going to be the next generation of their business. That's great, that's as you want it.

I think some of the concerns people have are will that process be hampered, will it be held up by undue intellectual property protections that are applied to DNA sequences prematurely before they are really ready to be developed? I think these concerns are actually somewhat less now than they were two or three years ago. When Dr. Varmus made the decision shortly after his arrival that the NIH would no longer seek patents on small bits of sequence of no known function; despite the fact that such patents had been filed, they were withdrawn. That I think inspired other parties to do the same. There was a concern that there might be a lot of very useful sequence information tied up in the private sector because a lot of private databases were being produced. Recently, Merck decided that for their own business plan this was not a good thing,

and so they funded a group at Washington University in St. Louis to produce a similar database but put it immediately in the public domain. Much of the information that you couldn't get a year ago you can now get easily.

So, I think at the moment the balance is about right. You would not want to make broad sweeping statements that patents should never be used for genes of any sort, because you would kill biotechnology in its tracks and that would be very bad for the American public. Similarly, I think you would not want to go out and protect every run of 10 base pairs with a patent because that would be ridiculous, and it would clearly hamper the development of that information into useful therapies. The topic deserves a lot of close attention and I have glossed over some of the specifics, but at the moment I think I would say things are going reasonably well in this regard. We're watching it closely.

This group of six large-scale sequencing centers that we funded two weeks ago have been told that as part of their evaluation we expect them not to have filed patents on large blocks of sequence from chromosomes. We don't think that would serve the public well and adherence to that guideline will be one of the criteria by which we evaluate their renewal applications.

Mr. MILLER. Thank you.

Mr. PORTER. Thank you, Mr. Miller. Before I recognize Mr. Wicker, I would like to welcome to the subcommittee Glinda Miller who is with her husband here today. I hope that your presence indicates a very strong interest in biomedical research because I have been attempting to plan a visit by members of the subcommittee and spouses to NIH. Maybe you would like to help us organize that. If you come to these meetings, you get work. [Laughter.]

Thank you for joining us today, Mrs. Miller. Mr. Wicker.

Mr. WICKER. I'll pass at this point, Mr. Chairman.

Mr. PORTER. Mr. Istook.

PATENTING AND AVAILABILITY OF INFORMATION

Mr. ISTOOK. Thank you, Mr. Chairman. Dr. Collins, I appreciate very much the work you're doing. I wanted to follow up a bit on what Mr. Miller was saying in the area of patents and intellectual property. Since this is being such a cutting-edge area of science and of biology, do you have any sort of overall review not only of—I don't know what the proper terminology is—what might be like a first tier of patents where you take a set of genes and try to establish a patent on them, or others that are, I'm going to use the term second-tier, involving different applications of those and different techniques, and which may, in many cases, spring out of either the research you've done directly or through the grants and contracts that you've let? What I really want to ask is, have you assembled any sort of overall review of these different levels and what patents have been established in the field and which are traceable or attributable to some sort of Federal funding? Is there such a general report, an overview?

Dr. COLLINS. Yes, there was a recent article published in "Nature Magazine" about three weeks ago which was a review worldwide of patenting of genes, reviewing some 1,400 or so patents which have been issued on gene sequences since the 1970s.

[CLERK'S NOTE.—Subsequent to the hearing, NCHGR corrected the figure to "1,200" for the record.]

This article indicates that in the U.S. there have been 39 patents issued to the U.S. Department of Health and Human Services and the NIH. There have been more issued to U.S. companies as well. As you might imagine, there have been a lot in Japan, but there have been relatively few in Europe, which caused the writers in "Nature Magazine," which is an English journal, to be somewhat concerned that they were missing the boat. You could argue that maybe they're the ones that have it right; I don't know, that's a matter of opinion.

The problem with that study is that while it is useful and interesting, it is rather dated because there is such a slow turnaround time for patents to issue. It is very difficult to get information on patents that have been applied for but not yet issued. The NIH knows about patents filed by its grantees because they are required to notify the NIH. I am sure the Office of Technology Transfer at the NIH could produce a roster of those, although there are some confidentiality issues that might inhibit to some degree the detail that could be provided. But that information is kept in one place.

Mr. ISTOOK. I'm interested in getting the overview. The Nature article, I don't know who compiled it. I take it from your comments it was not actually an NIH—

Dr. COLLINS. It was a European group.

Mr. ISTOOK. A European group. My main concern is, realizing that you've taken a very open approach to the technology and part of your purpose is to enable the technology to be transferred and utilized other places, but I would certainly like to make sure that the fact that NIH has a general openness is not seized upon by somebody else to try to come in behind and carve out an area or take advantage of some different procedure to somewhat undercut what you have done. But I would be interested if you could just assist us in whatever you have at NIH that helps provide an overview and make that available to us.

Dr. COLLINS. Certainly.

Mr. ISTOOK. That would be helpful.

[The information follows:]

OVERVIEW OF THE PATENTING AND AVAILABILITY OF INFORMATION

The National Institutes of Health encourages U.S. competitiveness both extramurally and intramurally. Various legislation ensures that research results can be translated to health benefits for Americans and that the rights of the inventors and the public investment is protected.

Research supported through grants or contracts

The Bayh-Dole Act encourages researchers to patent and market their inventions by guaranteeing patent rights. This Act automatically grants first rights to a patent for an invention fully or partially funded by a Federal agency to the university or grantee/contractor institution. To obtain these benefits, however, the inventor and the institution have several reporting requirements that protect the rights of the Government.

This landmark legislation is important because it gives nonprofit organizations and small business firms the right to elect to retain title to inventions. Its objective is to use the patent system to promote utilization of inventions arising from Federally supported research; to encourage maximum participation of small business firms in Federally supported research and development efforts; to promote collaboration between commercial and nonprofit organizations; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner that promotes free competition and enterprise; to promote commercialization and public availability of inventions made in the United States by United States industry and labor; and to ensure that the Government obtains sufficient rights in Federally supported inventions to prevent the unreasonable use of inventions.

Research supported in NIH intramural laboratories

The Federal Technology Transfer Act of 1986 (FTTA) and subsequent Executive Order 12591 (April 10, 1987) resulted from recognition that U.S. industrial competitiveness can be greatly enhanced if technology developed in Federal laboratories is commercialized by American industry. In order to stimulate this technology transfer, incentives are offered both for Federal scientists and laboratories and for collaborating companies. As a result, NIH has applied for and received numerous patents and licensed many inventions.

For example, in fiscal year 1994, NIH licensed 22 gene-related technologies, such as genes, cDNA, plasmids, and vectors. Sixteen of these technologies had patents or patent applications associated with them. The other 6 technologies were licensed without patent coverage. In fiscal year 1995, NIH licensed 14 gene-related technologies, 8 of which were associated with patents or patent applications.

Ownership of the human genome

S. M. Thomas, A. R. W. Davies, N. J. Birtwistle, S. M. Crowther and J. F. Burke

Despite wide interest in human genome patents, there has been little information about exactly who owns what. Europe would do well to ponder over the stake already held by Japan and the United States.

The patenting of human DNA sequences is the most controversial aspect of the Human Genome Project (HGP). Academic scientists strive to increase knowledge and to publish their findings. Companies, on the other hand, regard the exclusivity gained through patenting as essential to successful commercial exploitation of the HGP for new therapeutic and diagnostic tools. Public debate over the ethics of patenting DNA has become more and more intense over the past three years as the HGP has gathered pace. Many religious and environmental groups, as well as individual scientists, remain fundamentally opposed to the granting of patents^{1,2}. Despite wide interest in the subject and its importance for public policy, there has been a remarkable dearth of even basic information about the actual ownership of human DNA patents. Instead, attention has generally focused on a few specific and often controversial examples of gene patenting as, for example, in the case of genes involved in breast cancer (*BRCA1*, *BRCA2*), cystic fibrosis and obesity^{3,4}.

Here we comment on the results of a comprehensive analysis of patented human DNA sequences using the GENE-SEQ database (Derwent Ltd, UK, release no. 18). Our data reveal that between 1981 and 1995 a total of 1,175 patents for human DNA sequences were granted worldwide. Each patent in our study contains an average of only three DNA sequences. The legal interpretation of the patent determines whether it protects only the sequence(s) disclosed, or whether its scope covers all possible forms of the gene (an

extreme example being Genentech's patent on tissue plasminogen activator).

Ownership is overwhelmingly dominated by the private sector (Fig. 1). Not only have three-quarters of these patents been granted to industry, but most of the 213 companies involved are Japanese or US. Nearly half these privately held patents are Japanese-owned, the others being divided almost equally between companies from the United States and the rest of the world. By contrast, the public sector is markedly under-represented. Only 17 per cent of the total have been granted to public institutions, and most of these are US.

Only the European Patent Office (EPO), the US Patent Office (USPO) and the Japanese Patent Office have issued significant numbers of patents. That half the world total is from the EPO is largely because both the United States and Japan have been vigorously patenting human DNA in Europe. Together these two countries own about 70 per cent of all EPO patents for human DNA sequences. Japan owns a third and the US nearly 40 per cent. Europe, on the other hand, has performed poorly, with only 24 per cent. Industrial investment has done much to boost the EPO total: more than 80 per cent are company-owned. Given that the United States has generally taken the lead in human genomics, it is surprising that only 16 per cent of human DNA sequence patents have been issued by the USPO. The paucity probably results from a backlog of biotechnology patent applications — a feature of the USPO over the past decade⁵. As

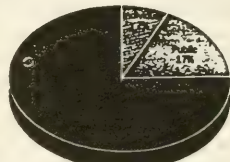


FIG. 1 Ownership of human DNA sequence patents. Includes all patents worldwide.

the situation improves, the number of USPO patents issued for human DNA sequences as a proportion of the world total is likely to increase because the United States is still viewed as the most important technological market for major inventions⁶. Only 41 per cent of USPO patents are privately owned and nearly all these belong to US companies.

The innovative character of small US firms dedicated to biotechnology is clearly reflected in our analysis (see table). Of the large US pharmaceutical companies, only three hold more than ten patents. In Europe, the situation is almost completely reversed. Large companies have been fairly active whereas the small-firm sector holds almost no patents. Remarkably, 88 Japanese companies own EPO patents for human DNA sequences. Although Japanese patents are generally narrower in their claims than USPO or EPO patents, the number of EPO patents held by companies such as Takeda is high at 44 (out of its world total of 63). Nevertheless, the Japanese consider their genome research to be lagging behind that of Europe and the United States by some five years.

Public-sector institutions in the United States own more than half of all USPO human DNA sequence patents and 59 per cent of publicly owned EPO patents. This is most probably due to the different institutional cultures of the United States, Europe and Japan. In the United States, public-sector scientists have for several years been encouraged to assess the patentability of their research results. Well-developed collaboration between US universities and industry and an environment that fosters academic entrepreneurs have undoubtedly stimulated patenting in the public sector. Why have European

PATENT OWNERSHIP OF PUBLIC AND PRIVATE SECTOR ORGANIZATIONS					
Private company	Country of origin	No. of patents	Public institution	Country of origin	No. of patents
Takeda	J	63	US Department of Health and Human Service	US	28
Genentech	US	41	University of California	US	13
Immunes	US	23	National Institutes of Health	US	11
Teyn	J	23	University of Washington	US	11
Hoffmann-La Roche	S	18	University of Texas	US	7
Ciba-Geigy	S	16	Japanese Foundation for Cancer Research	J	6
Sumitomo	J	18	New York State University	US	6
Cetus	US	16	Agency of Industry, Science and Technology	J	5
El Lilly	US	15	Salk Institute	F	5
Shionogi	J	15	Pasteur Institute		
Ashai	J	15			
Green Cross	J	15			

Includes all human DNA sequence patents granted worldwide. Where patent ownership is shared between two or more organizations, it is assumed that collaborators contributed equally. For the purpose of quantitative analysis, each party was therefore assigned an equal fraction of a patent. Countries of origin: J, Japan; US, United States; F, France; S, Switzerland.

COMMENTARY

institutions not been more active in applying for patents on human DNA? Many scientists in the public sector would argue that it is not their role to take the first steps towards commercialization of basic research. Further, some see the identification, isolation and cloning of human DNA sequences as pre-competitive. The traditionally poor links between universities and industry in the United Kingdom and other parts of Europe have also no doubt played a part in the low level of European public-sector patenting. In Japan, university researchers are not only prohibited by law from participating in research based in industrial laboratories, but government financial regulations inhibit interaction between universities and industry.

So what human DNA sequences have

currently acceptable under patent law provided that the usual criteria for novelty, non-obviousness and utility are met. Nucleic acids do not have any kind of exemption simply because they are the chemical compounds that form the basis of inheritance. As a result, more than a thousand patents for human DNA sequences have already been granted to nearly 300 organizations. The incentive to patent has been and continues to be industrial competitiveness for novel therapies and diagnostics based on specific DNA sequences. Industry, long aware of the critical importance of patenting in drug development, has provided the main impetus. Nevertheless, institutions in the public sector, particularly in the United States, are following the same path. The value of this approach

has been borne out by the judgement in *Amgen v. Genetics Institute*, which concluded that inclusion of DNA sequence information in patent claims was essential to secure intellectual property rights to erythropoietin, currently biotechnology's highest-earning drug at \$1.5 billion a year.

While Europe has over the past eight years debated the pros and cons of a harmonized directive on biotechnology intellectual property rights, Japan and the United States have between them secured rights to 70 per cent of EPO patents for human DNA sequences. That Europe's share of these EPO patents is so small is a major cause for concern. Foreign applicants are probably attracted to Europe because of its relatively new and less cumbersome EPO system, which processes patents within two years and is cheaper than the US system. Despite their vocal public opposition to biotechnology patents, European 'greens' have had little influence on patenting of DNA sequences (as opposed to plants and animals) in Europe.

What is not in question is European investment and competence in genomics. Although the European Union has spent some ECU75 million on genome projects, strong commitment to early release of sequence data into the public domain, rather than patenting, has been its priority. The shifting divide between public- and private-sector sequencing is nowhere more clearly illustrated than in the recent events surrounding the release of the full (that is, genomic) DNA sequence containing the breast cancer susceptibility gene *BRCA2*. Viewed as 'pre-competitive' information, and put on the Internet by the Sanger Centre at Cambridge, England, and the University of Washington, St Louis, it was rapidly exploited by the US company Myriad Genetics to locate the gene and file a patent for all diagnostic and therapeutic applications¹. Putting sequence information in the

public domain at the earliest opportunity will promote research in the public sector and accelerate gene identification and, inevitably, subsequent patent filing by industry. Novel sequence information alone is pre-competitive and unpatentable. Combined with utility and inventiveness, it can qualify as a patentable invention. That a US genome company (a sector almost absent from Europe) is enabled to file for a patent by the agency of publicly funded research in the United Kingdom sits uncomfortably with UK government policy on wealth creation through basic science.

Challenges to utility have been largely confined to the controversy over the rejected patent application filed by the US National Institutes of Health in 1991 for 1,250 partial human gene sequences or 'expression sequence tags'. But the criteria for scope and inventiveness of patents have become hotly contested issues². Given, as we see here, that DNA sequences are widely accepted as inventions and that patenting of human genes has been endorsed by the Human Genome Organization, it is unrealistic and impractical to seek alternative systems of protection such as copyright. Instead, attention and energy must be given to restricting the scope of patents so that the prospect of one company having proprietary rights over an entire gene and its mutations for all diagnostic and therapeutic purposes is no longer a reality. Public interest would be better served by policies encouraging competitiveness for improved second-generation healthcare products. Finally, it has been argued that it is obvious and no longer inventive to clone genes. In general, the law has been generous and ruled that cloning is indeed inventive. With the isolation of many new disease-related genes by the use of techniques of differential gene expression, the number of sequences for which patents will be filed will increase dramatically over the next three years. But as gene-cloning procedures become more standardized, patenting genes may well become more difficult. Rightly so. Meanwhile, Europe would do well to ponder over the stake that Japan and the United States already have in owning the human genome.

S. M. Thomas, A. R. W. Davies, N. J. Birtwistle, S. M. Crowther (Science Policy Research Unit) and J. F. Burke (Department of Biochemistry) are at the University of Sussex, Falmer, Brighton BN1 9RF, UK.

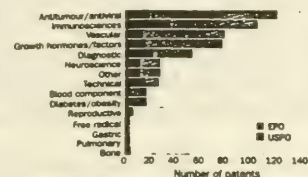


FIG. 2 Classification of human gene patents.

been patented? They range from primers for diagnostic use to patents for synthetic hybrids of interleukin and interferon genes. We divided the DNA sequences from the USPO and the EPO into 12 main categories (Fig. 2). The research areas covered by USPO patents are broadly similar in emphasis to those specified by EPO patents, although there is some variation. The category with the most patents overall is antitumour/antiviral, followed closely by immunoscience, growth hormones/growth factors and vascular categories. The combined first ranking of the antitumour/antiviral category emphasizes the importance of this research area for pharmaceutical companies; the category includes 58 EPO patents for sequences coding for interferons, interferon receptors and enzymes in the signalling pathway. And the dominance of the immunosciences in human DNA patenting is due to the early cloning successes with many natural and engineered genes for interleukins and their receptors. These products have therapeutic potential in stimulating the immune system and treating common allergies, as well as chronic diseases such as arthritis. About half the sequences in the EPO component of this category are for interleukin genes. Overall, the data show that the same therapeutic goals are being pursued by a wide range of companies.

Patenting DNA from any species is

1. Cole-Turner, R. *Science* 278, 52 (1995).

2. Olson, D. *Nature* 378, 425 (1995).

3. *Science* 268, 208-210 (1994).

4. Olson, D. *Nature* 378, 574 (1995).

5. Office of Technology Assessment. *Biotechnology in a*

Global Economy (OTA, Washington DC, 1992).

6. European Commission. *The European Report on Science*

and Technology Indicators, 1994 (EUR15897, Brussels, 1994).

7. Sambrook, D. *Nature* 372, 731 (1994).

8. Thomas, S. M., Kunita, H. & Burke, J. F. *Res. Pol.* 24, 645-663 (1995).

Dr. COLLINS. The Bayh-Dole Act assigns to universities who are our grantees the main responsibility to seek rights to patents which are produced as a result of NIH funding. I think that system has promoted a fairly vigorous approach to patenting. Many universities have very active offices doing this sort of thing. But we would be happy to provide that kind of information.

Mr. ISTOOK. That would be very helpful. Thank you. Thank you, Mr. Chairman.

DATABASES AND AVAILABILITY OF INFORMATION

Mr. PORTER. Thank you, Mr. Istook. Dr. Collins, Daniel Cohen, one of the French pioneers in genome research, has left his government research center for a biotechnology company saying that private industry is the wave of the future in genome research and that 70 to 80 percent of all the data is in the private sector now. If it is true that so much data is held privately, we will face a situation where research will be thwarted because some genome sequences will be proprietary, or will the Federal Government have to finance research repeating the work of private firms so that the data is accessible?

Dr. COLLINS. Professor Cohen is certainly a colorful figure and everything he says comes across as being rather controversial. This statement is no exception. Yes, he has gone on to work for GenSet which is a company in France. I think his comments might have been closer to true a year and a half or two years ago than they are now. I mentioned the initiative by Merck to fund a publicly available database of what are called ESTs, expressed sequence tags, which are the part of the genome that is actually expressed into RNA and then into protein. This is the part that some people would argue has the most information value. It is true that a number of companies, GenSet among them, have been interested in generating such databases and keeping that information secret because that is their business investment. That has been a strategy which several companies have been following, and I am sure they have in the process identified useful sequences. In the U.S., Human Genome Sciences recently announced the issuing of three patents to them based upon sequences that they obtained in this way.

I think the concern your question reflects is one that people in the scientific community share. Will this whole effort have to be re-initiated in order for the public scientific effort to have access to the information? The Merck effort has largely made that unnecessary and that was private money. For the total genome sequence, not the small part of it that is represented as ESTs, but the whole thing, all 3 billion base pairs, there is as far as I can tell no interest in the private sector in doing that kind of sequencing. That's too far away from what they can see as an intellectual property, too far away from a product, and they are cheering on the effort of the Federal Government in the U.S. and other countries as well to do that part. I don't think we're going to see a competitive private effort.

Mr. PORTER. Does the Federal Government have any tools other than the power of persuasion to force the release of privately held data so that you can avoid duplication?

Dr. COLLINS. I think if that sequence has been produced by a company using their own resources and they decide to keep it private, it would probably be improper for the Federal Government to step in and say oh, no you don't. I think that would be violating basic principles of non-interference. So I would say the answer is no, there are no other tools other than persuasion.

PUBLIC-PRIVATE COOPERATION

Mr. PORTER. In Japan the government agency MITI has initiated a joint research effort with industry focusing on gene function and automated screening equipment with the Japanese government supporting 70 percent of the cost and industry putting up the remaining 30 percent. Are there any comparable cost-sharing efforts underway in the United States?

Dr. COLLINS. Yes, there are. I just mentioned one and, again, I keep coming back to this Merck effort because there you have a business enterprise which is funding an academic laboratory to produce sequences which are put in the public domain. There are other instances where we are in partnerships with private companies and universities to carry out particular kinds of technology. There's a company called Affymetrix in California, for instance, which largely came into being because of an NCHGR grant. Now they are working on DNA chips to apply to diagnostics. So such partnerships do exist. Another recent example, not with a private company, but with a foundation, is the Howard Hughes Medical Institute. HHMI has recently decided to fund the sequencing of large numbers of mouse ESTs over the course of the next year. So we will have that database of information and the Federal Government doesn't have to pay for it.

You mentioned Japan. The Japanese genome program has been growing more rapidly than any other in the world for the last two or three years. They started out at a lower level but are rising quickly. I had the chance to meet with Professor Ken-ichi Matsubara and Professor Yoshiyuki Sakaki, the two leaders of that effort, in Germany a couple of weeks ago. It was a very encouraging conversation in that they also intend to make their sequence data public if it comes out of their genome sequencing effort, and they intend to avoid duplication of effort. That is gratifying to hear.

NON-MEDICAL USE OF GENETIC INFORMATION

Mr. PORTER. That was my next question. Your center sponsored the somewhat controversial conference last fall on possible genetic bases for criminal behavior. How would you characterize the outcome of that conference? Do you plan to sponsor any additional work in this area?

Dr. COLLINS. That conference, obviously created a great deal of public interest. In its initial manifestation it was felt to have been advertised in a way that was offensive to some people. The conference had to be cancelled and then restarted after a great deal of consideration by NCHGR and our advisors. The conference was still somewhat difficult to carry off. Because of the public attention that had been attracted to this, there were some folks who showed up with signs to protest and it was a bit difficult to actually carry out a discussion of the issues. It is unfortunate that this kind of

atmosphere seems to have surrounded this topic. Realistically however, when one begins to talk about genetic contributions to criminal behavior, this is very delicate territory and well-intentioned people may feel quite strongly that this is the kind of discussion which can have unfortunate overtones which sound, in many ways, as though they are making social commentary rather than biological commentary. We were all sensitized to that.

The ELSI Working Group, which has been a very important part of our policy deliberations, is anxious to pursue an overlapping area; namely, the non-medical uses of genetics. It is astounding these days the degree to which a "gene for this" and a "gene for that" has found its way into common parlance. Even high ranking political figures are saying I must have the gene for liking sports cars. "Time Magazine" on the newsstand last summer had a cover that says "Infidelity: It's in Our Genes." How many people looked at that cover that week and said, Oh, good, I thought it was me, and it was really my DNA's fault. This is ridiculous. We are ascribing powers to the double helix that we really ought not to when it comes to areas of human behavior. And yet it is a natural human tendency to be reductionist, and I guess we're falling into that. Clearly, that's a topic that needs attention.

My own sense is that all of the predictions about the study of the genetics of criminal behavior being destabilizing are a bit overstated. After all, many of us in this room have a gene which places us at a tenfold increased risk of getting into trouble with the law. I have that gene. So do you. It is having a Y chromosome. [Laughter.]

That fact has not led to a collapse of our social fabric. We've managed to deal with that. Whatever other genes we find that may in some small way contribute to criminal behavior are probably not going to be nearly as strong as the Y chromosome.

Mr. PORTER. We're all just victims of our DNA. [Laughter.]

Ms. Lowey.

GENETIC TESTING FOR BREAST CANCER

Ms. LOWEY. Thank you, Mr. Chairman. Dr. Collins, on the BRCA1, my understanding is that the blood test for the BRCA1 gene in Ashkenazi Jews is a simple blood test and that private companies have already begun to market the test to women and their doctors. To what extent is the test now available to the public? I would be interested in knowing your concerns regarding the availability of the test at this time. Is there a legislative role for Congress? Is there a role for the FDA? Could you discuss that with us.

Dr. COLLINS. Those are all very good questions and ones that I'm deeply concerned about. There is at least one company that has announced they are testing for the so-called 185 deletion AG mutation, the Jewish mutation, in BRCA1. It is a company in this general geographic area. They are offering some genetic counselling with the test, which is absolutely essential. But it does create some concern when that test is being marketed to primary care physicians, who may not be in possession of a lot the details of the pros and cons of testing.

Why would somebody not want to know? Some people would argue this is potentially very valuable information. But I don't think any woman should go through this kind of testing without first having a chance to learn the pros and cons. It is possible, by finding you're at risk, that a woman with a BRCA1 mutation might be able to reduce that risk, for instance by intensive mammograms beginning at an earlier age than usual. But we don't have good enough data to know just how valuable that surveillance will be. We need that data urgently. What about more drastic procedures like prophylactic mastectomy or removal of the ovaries? There are troubling examples of women who have done that and yet still developed cancer in the small amount of epithelial tissue that remains after the surgery. There are not good answers to give to women found to carry a mutation about what they should do. That is something every woman considering this needs to know, that you may be walking in to a situation where you find out you're at risk but the options you have available are rather blurry.

There is also a major concern about discrimination where you find out you're at high risk and the next day you lose your health insurance. Losing your health insurance if you are at risk for breast cancer can be a lethal event. If you don't have the resources to protect yourself, then this is not information that's going to benefit you. We do not have adequate protections against genetic discrimination yet. I think there is a place for legislation in that situation and I am delighted that the House and the Senate are stepping up to the plate on that.

TASK FORCE ON GENETIC TESTING

Should the Food and Drug Administration take a role here? Should somebody tell the company that is offering this to stop? Well, that's being hotly deliberated right now in several settings. It is being talked about in the professional genetics community. Should there be professional standards that basically say physicians shouldn't do this? Or should one be more heavy-handed, bring in the regulators, the FDA, the Health Care Financing Administration, other agencies that have responsibility for laboratory testing? It is not a popular concept in the current climate to talk about adding additional regulations. But an NCHGR established Task Force on Genetic Testing, which is meeting this year to deliberate about these issues, certainly has not ruled out suggesting that option. And as the Task Force goes from the draft principles, which they have just issued, to implementation, which is their next step, it's going to be very interesting to see what they recommend. Do we need a special panel to decide when a test is ready for clinical practice? I think that's a serious consideration. This kind of genetic test information can be toxic as well as beneficial. If this were a new drug, you wouldn't take it directly out of the chemistry lab and give it to a patient. You would try it out first in a clinical trial and I think there is a strong argument for doing that for testing.

The NCHGR, in collaboration with the National Cancer Institute and the National Institute of Nursing Research and the National Institute of Mental Health, has been carrying out a small cooperative trial of breast and colon cancer testing for the last year. This was actually started slightly before BRCA1 was cloned. We were

out ahead on this one. We learned a lot about how to do this in ways that, after the fact, women said that's the kind of information I needed, that helped me make up my mind. But we're now in a position of needing to expand those trials. I am delighted that the National Cancer Institute has made a decision to set up a National Cancer Genetics Network which will be available to physicians and patients who are interested in genetic testing for cancer. It will do it in a fashion that includes full informed consent and full review of the protocol by an institutional review board. The Network will collect information about who asked for testing, who went through with testing, and what happened to them, so that five years from now we'll have answers to these questions about what it means to have a BRCA1 mutation. All of this will be done in a research trial, but in a way that expands access for the many women who are interested in this and who currently can't find a protocol that's willing to sign them up. I think that's the answer. It is not really correct to say we have a dilemma here between two opposing extremes. I think this solution basically takes care of all the points of view. And I am very enthusiastic about seeing the Network move forward and I suspect Doctor Richard Klausner may very well talk about that tomorrow.

Mr. PORTER. Thank you, Ms. Lowey. Mr. Miller.

Mr. MILLER. I have other questions but I think for the sake of time I will pass. I was going to ask a question of intramural versus extramural research, do we have time?

Mr. PORTER. Yes.

INTRAMURAL RESEARCH

Mr. MILLER. Okay. Perhaps if I were here a couple of years ago I would have asked the question, but there was a shift to add a lot more intramural research starting in 1994. Now, it is about 25 percent of your research budget, is that right?

Dr. COLLINS. Yes.

Mr. MILLER. Was that intended? And what is the explanation or rationale of why intramural versus extramural?

Dr. COLLINS. NCHGR was first started as an office in the Office of the Director and then it became a National center. There was no intramural program for the first three years of this effort. The decision was made, and this predated my arrival on the scene, that it would be very useful to have on the NIH campus a hub of activity in human molecular genetics. The NIH campus is enormously strong in many areas of medical research but a core group of researchers whose approach to problems were genetic ones was missing. It seemed like a natural for the National Center for Human Genome Research to initiate that effort. The size of the intramural program basically was predicated upon the issue of critical mass. If you're going to initiate such a program, you need expertise in areas like gene discovery, mouse models for disease, diagnostic development, and gene therapy. Those are all now vigorously active under the umbrella of this intramural program for NCHGR. It therefore ramped up very quickly over the course of two years and has now reached equilibrium and is not anticipated to grow larger.

The philosophy of the intramural program of NCHGR is very different than the extramural program. The extramural program

funds maps and sequences and technology and all of the infrastructure that the rest of the community is really interested in getting as quickly as possible to catalyze gene discoveries and their applications. The intramural program is applying genome research to the study of disease, within the confines of the NIH. This program has been quite a success. Counting them up, there are at least 150 [CLERK'S NOTE.—Subsequent to the hearing. NCHGR corrected this figure to "190" for the record.] collaborations now going on between that component of NCHGR and investigators both at NIH and in universities and, in fact, around the world. So dollar for dollar, it has been a very good investment.

Mr. MILLER. Thank you.

Mr. PORTER. Mr. Istook.

Mr. ISTOOK. I have no further oral questions. Thank you, Mr. Chairman. Thank you, Dr. Collins.

Mr. PORTER. Ms. Lowey I know has another question or two. I have one I am going to ask and then I'll call on you, Ms. Lowey, and anyone else who would like to ask one more.

Ms. LOWEY. That's fine. I just want to follow up on a couple of points.

Mr. PORTER. Can you tell us more about the statement in your testimony that some day science will be studying the expression patterns of thousands of genes at once. We've become accustomed to thinking about the importance of individual genes for diseases. But does this mean that answers to diseases are most likely dependent on understanding a large group of genes and their interaction?

GENES STUDIED WITHIN A NETWORK

Dr. COLLINS. That's a great question. Yes, I think interactions between genes will be important for many complex diseases, things like diabetes, coronary artery disease and hypertension. These are not due to the action of a single gene gone awry, but several genes, each one of which has a mild effect. When you pile them all up together they can result in the appearance of a disease. That is, in fact, the kind of genetics which we are now getting into in a big way with the genetic maps and the technologies that are available. The genetics of juvenile onset diabetes, for instance, that you heard about this morning, has made wonderful advances as a consequence of these genetic maps.

What we're headed towards, and what your question refers to is the chance to actually look, once the genome sequence is in hand, and see what's happening to all 100,000 genes at one time. People have on the drawing boards methodologies that would allow you to do that. They depend, most of them, on the concept of using chips. These are silicon wafers, onto which at very high density DNA sequences are arrayed that represent each of those 100,000 genes. The RNA, the expressed part from a tissue or a cell, can be labelled with some fluorescent material. Then you hybridize it to that chip. Everywhere there is a match it will stick, and where there isn't, it won't. How much RNA there is will determine how bright the signal is. It should be possible to do experiments where you look at the whole tapestry of genetic expression in one experiment over the course of time as a function of whether this was a normal cell

or a cell from somebody with a particular disease, as a function of whether you have manipulated the system by adding something to that cell, and deduce from that sort of experiment which gene is talking to which in the cell.

This is going to be a kind of biology that we never dreamed of. This really is where the Human Genome Project is going. Once we have the full sequence, what are we going to do with it? It is not too soon to begin thinking about that. Already, the yeast people will be thinking about that after 10:00 a.m. tomorrow when their sequence is announced, and the human researchers only have to wait another seven to nine years to be in the same boat. We don't want to be in the situation where suddenly we're there, and it's like what do we do now. There's a wonderful quote from Wayne Gretsky. Gretsky was asked how is it that you're such a good hockey player. And he said, well, it's very simple; "I skate where the puck is going to be." And that's what we would like to do too.

Mr. PORTER. Thank you. Ms. Lowey.

GENETIC TESTING FOR BREAST CANCER

Ms. LOWEY. Thank you, Mr. Chairman. Dr. Collins, as you can see, I am very concerned about how we keep doctors, genetic counsellors, and other health professionals informed of the leaping discoveries in this Genome Project. I believe that in your testimony you state that a new grant solicitation will encourage researchers to submit applications for projects. I have two questions. Number one, in terms of the commercial company or doctor or organization that's offering this test to the public and that you said is voluntarily offering genetic counselling, have you been able to get any feedback, I assume the counselling is voluntary from this entity, I'm not sure if it's a business or a doctor—

Dr. COLLINS. It's a business run by a doctor.

Ms. LOWEY. What control do we have related to this entity? And secondly, is there money sufficient to provide for the training of doctors, genetic counsellors, and health practitioners? I see this, in addition to the insurance question, as an overwhelming challenge for the NIH and for all of us.

Dr. COLLINS. I agree. With regard to the company, there are currently no clear march-in rights that any governmental agency has under present interpretations of authority. You could argue maybe FDA has the authority, but they have chosen not to use it in this circumstance. The company is run by a physician. One does have some concerns that this is a company that's set up to make money and can you in fact be sure that genetic counselling is going to be provided in an unbiased way by an organization that has an investment in having as many women as possible being tested? That's how they are going to make a profit. If they counsel a woman before doing the test and she decides not to have the test, the profit just went down. Many are concerned that there should be a separation between medical advice and profit, and it is not in place in this instance. This has certainly brought to the forefront the need for something like this National Cancer Genetics Network and also the need for professional standards, to basically marginalize the outliers.

Education of health professionals is a critical part of the solution to this dilemma. Again, it is interesting you asked the question because I spent all of this morning meeting with representatives of the American Medical Association and the American Nursing Association about setting up what we would like to call a Coalition for Health Professional Education in Genetics. This will be a national interdisciplinary coalition which will get educational information into the hands of practicing physicians and nurses and other allied health professionals to allow them to become deliverers of genetic services in responsible and well-informed ways. We don't intend to waste time getting that going. The National Cancer Genetics Network will need to do this for cancer genetics for all of its participants, so that will be a good pilot project. I agree, we need to move on this, and that is a very high priority right now for our ELSI program.

Ms. LOWEY. How much money has been allocated for this grant and is it sufficient?

Dr. COLLINS. The ELSI program is currently 5 percent of the NCHGR budget. That covers a broad range of priorities, only one of which is education. In the educational arena, health professional education is our highest priority. At the present time, we are driven to some extent by the grants which we receive. We are funding in the ELSI program, like the rest of the NIH, about 15 to 20 percent of our approved grants, so many things get turned away. We could obviously invest more if we had the capacity to do so. These are always tough trade-offs.

I am hoping through the Coalition that I mentioned to also bring in other sources of funding besides the Federal Government, foundations that are interested in professional education, organizations like the AMA and the ANA.

Ms. LOWEY. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Lowey. Any final questions, Mr. Miller?

Mr. MILLER. No, Mr. Chairman.

Mr. PORTER. Mr. Istook?

Mr. ISTOOK. Nothing further, Mr. Chairman.

BEYOND THE FIRST COMPLETED HUMAN GENOME

Mr. PORTER. I have one final question bearing on your answer to my last question, and that is, are we going to have the Human Genome Project II? In other words, after you are finished with all the mapping, are we going to then start working, or is that work that would be done within the individual institutes?

Dr. COLLINS. It is a question which is beginning to be discussed and I don't think the answer is completely clear. I think the scientific community will need to weigh in on this over the course of the next couple of years. Those who have looked at it so far, and they aren't just people like me from NCHGR, have concluded that there are at least four or five areas of genome-based research that will need to continue to have a home even after the first human DNA sequence has been obtained.

One area will be technology. We're going to continue to want to do more sequencing. Once we get one genome sequence done, we're going to want to do 100 more to see what the comparisons look

like. So we're going to keep wanting to drive the price down and have better technology so that you can do sequencing on a credit card size chip instead of a big, bulky instrument. Demand for sequence information, like computer science, is going to be insatiable and we need to try to do what we can to meet it. I think a special part of NIH will need to encourage that. Then there's the whole business of evolutionary biology, that is the comparison between genome sequences of many different species. Again, I think that will do well if it has a home. Population biology, where you look at many different human sequences is another area which would be well served by having some central location. Maybe most importantly, the elucidation of gene function where you look at all 100,000 genes at once, not just to see what levels they are being expressed at, but how do they work, how do they talk to each other. Can you knock them out in a model organism in a systematic large-scale way instead of one-gene, one-graduate student at a time, which is the way we currently do it.

And then there are the ELSI issues. They are not going to go away. I am optimistic we will take care of some of the major dilemmas of today but there will be new dilemmas of tomorrow. I think the ELSI program has been successful, and will need to have some permanence.

So, the likely outcome is we will be looking at a phase II of the Human Genome Project after that first sequence is done. It will look somewhat different but it will be very exciting, and I think it will be a very good investment for NIH to continue to support that.

Mr. PORTER. Well, we hope at that time we can still call you Dr. Ahead of Schedule and Under Budget, as we do now. Thank you for the excellent job you're doing, Doctor Collins, and thank you also for your excellent testimony here today.

Dr. COLLINS. Thank you, Mr. Chairman.

[The following questions were submitted to be answered for the record:]

GENOME PROGRAM AT THE DEPARTMENT OF AGRICULTURE

Mr. Porter: The Department of Agriculture funds genomic research. Are there any common links either in technique or subjects between your work and theirs?

Dr. Collins: The USDA supports research to study the genomes of agriculturally important plants and animals. Their plant genome program aims to foster research that identifies, characterizes, and manipulates genes that control plant traits important in agriculture and forestry. USDA is also a participant in the interagency initiative to sequence the genome of *Arabidopsis thaliana*, a member of the mustard family which is commonly used in plant research; this will be the first plant genome to be completely sequenced. The USDA animal genetics programs support genetic research in cattle, sheep, pigs, poultry and aquaculture.

Much of the technology for genomic mapping and DNA sequencing that is being used in USDA-supported genome research was actually developed as part of the Human Genome Project. Technology development has been, and continues to be, a key component of the NCHGR research program, in part because this is needed for human genome analysis and, in part, because the new technologies will generally be applicable to the study of other genomes as well. NCHGR's mapping and sequencing effort is limited to the study of the human genome and the genomes of a select set of model organisms, which were chosen because of the extensive amount of genetic information known about these organisms, making them the most valuable of the non-human systems in contributing to our understanding of human genetics. Therefore, at present, the NCHGR and USDA genome programs are not studying the same organisms nor are they expected to do so in the future, but the common technology ties our efforts together.

GENETIC RESEARCH AT NIH

Mr. Porter: How much funding is devoted to genetic research throughout the NIH other than at your Center? Do you play any coordinating role or identify priorities in genetic research expenditures across campus?

Dr. Collins: In FY 1995, total NIH support for gene mapping research was \$659,016,000. Estimates for FY 1996 and FY 1997 are \$702,015,000 and \$718,959,000 respectively.

While not having a formal role in coordinating extramural research in genetics, there are an increasing number of examples of specific programs--e.g., the analysis of the rat genome; the studies of the introduction of genetic tests for cystic fibrosis and for breast and colon cancer into clinical practice--in which NCHGR has coordinated its activities with those of other institutes. NCHGR extramural staff have also served as consultants for other institutes--and other federal agencies--in scientific areas related to the application of genomic technologies, such as DNA sequencing. Finally, NCHGR extramural staff have recently initiated a series of

on-going discussions with staff of other institutes about the impact that genomic science will have on future approaches to a wide range of biomedical research problems.

Central to the mission of the intramural program in NCHGR is fostering productive collaborations with other human genetics research projects at the NIH, thereby complementing ongoing activities in human molecular genetics, structural biology, and gene therapy. The NCHGR provides this coordination for intramural genetics research across the NIH in several important ways. During FY 1995, NCHGR scientists formed or continued a total of 190 collaborations of which 52 were with scientists on the NIH campus.

Scientists in NCHGR collaborate and consult with many NIH investigators studying the genetic components of cardiovascular disease, psychiatric illness, neurological disease, cancer, and pigmentation disorders. They serve as genetics experts on panels of intramural and extramural NIH scientists discussing strategies for genetics research in the areas of autoimmune disease, osteoporosis, Parkinson's disease, autism, the genetics of aging, and the genetics of alcoholism.

The intramural program of NCHGR, which established the Genetics Interest Group (GIG), coordinates the activities of this NIH-wide group of scientists who meet once a month to present research results. The GIG is also responsible for bringing three world-renowned lecturers each year to the NIH Wednesday Afternoon Lecture Series. The NCHGR intramural program also coordinates the Medical Genetics Training Program, which is a major training and research effort for MD and PhD fellows that focuses on the clinical aspects of genetics.

The NCHGR also sponsors a gene therapy interest group. This is an inter-institute intramural seminar-discussion group that meets twice each month to hear formal seminar presentations from both intramural NIH scientists as well as non-NIH scientists--both academic and industrial. The group was organized in April of 1995 and is open to all NIH investigators as well as investigators in the Washington, DC area who are interested in gene therapy. We have over 200 registered participants in the group including some from local biotechnology companies and even members from NIEHS in North Carolina. In addition to our regular meetings, a WEB page for the group is being prepared and regular information bulletins are sent to those registered. The intention of the group is to provide a forum for NIH scientists for exchange of information and to foster collaborations that are not restricted by traditional Institute borders.

The NCHGR intramural faculty created, implemented, and supported parallel computing for advanced genetic linkage analysis through the NIH Division of Computer Research and Technology. The facility is open to all NIH intramural scientists who have a need for fast, parallel-processing-based linkage analysis of pedigrees. The NCHGR computer facility houses and supports three electronic mail listservers used campus-wide as electronic "bulletin boards." NIH scientists can use these electronic bulletin boards to advertise seminars of interest to geneticists, to ask

questions or help in scientific collaborations, and to advertise postdoctoral opportunities in genetics research. These listservers include the Genetics Interest Group listserv, a clinical genetics listserv, and a genetics and ethics listserv.

As a resource for the NIH community, the NCHGR provides expertise in genetic and physical mapping through a series of resource facilities for genotyping and genetic analysis of large families. The physical mapping resource serves as a repository for DNA clones and libraries.

INTERNATIONAL FUNDING OF THE HUMAN GENOME PROJECT

Mr. Porter: How much funding are other countries contributing to the Human Genome Project?

Dr. Collins: The following table represents estimates only for the foreign programs. Budgets continue to change due to political decisions. Different countries have different fiscal years, so some fiscal years overlap calendar years; we have not attempted to divide the budgets of all countries into a comparable fiscal year period.

For comparison purposes, two important points need to be taken into account. First, salary and other overhead costs, which represent a significant portion of the costs of the NIH genome program, are generally not included in the international budgets. Second, each of the programs have different definitions for "genome research" which also complicates an easy comparison of international funding. Most of these programs do not include support for research on the genomes of model organisms, which is a significant component of the NCHGR program. On the other hand, some of these programs include classical human genetics research and research on genetic diseases, which are not specifically included in the NCHGR program. Many other countries are contributing to the Human Genome Project, but to a smaller degree. These include Sweden, Belgium, Denmark, China, Korea, Germany, India, the Soviet Union, the Netherlands, and others.

INTERNATIONAL FUNDING FOR HUMAN GENOME RESEARCH
(U.S. dollar equivalent in millions)

	<u>1989</u>	<u>1990</u>	<u>1991</u>	<u>1992</u>	<u>1993</u>	<u>1994</u>	<u>1995</u>	<u>1996</u>
United States*	46.7	86.7	134.8	166.2	169.3	170.9	182.6	199.9
European Union (EU)	2.6	7.7	10.8	10.5	22.8	17.9	17.9	35.8
France				10.0	10.0	8.0	8.0	8.0
Italy	0.9	0.9	1.5	1.5	1.2	1.2	1.2	
Canada					1.7	2.7	4	4
Japan	8.8	12.4	23.3	30.6	40.4	44.8	51.2	52.2
United Kingdom	3.3	3.3	3.3	7.1	9.5	17.4	50.1	50.1
Estimated total	62.3	111	173.7	225.9	254.9	262.9	315.0	350.0

Footnote: Rough estimates only due to difficulties in comparing dissimilar programs.

* NIH and DOE

CENTER FOR INHERITED DISEASE RESEARCH

Mr. Porter: Are you planning to open a new research center in Baltimore?

Dr. Collins: The NCHGR, in partnership with six NIH Institutes and an academic institution, plans to establish a center to assist both extramural and intramural investigators pursuing the genetics of common diseases. The main objective of the center will be the identification of the genes that play important roles in diseases, like diabetes, cancer, neurogenetic disorders, etc. It is envisioned that the activities of the center will fall into five interdependent components: (1) Statistical Genetics; (2) Genetic Epidemiology; (3) Medical Informatics and Database Management; (4) Genotyping; and (5) Technology Development.

IDENTIFICATION OF MOUSE GENES

Mr. Porter: The Howard Hughes Medical Institute announced it would commit \$2.3 million to a project to identify molecular identifiers from mouse tissue in order to reconstruct entire mouse genes, with the ultimate goal of creating mouse models of human genetic diseases. Why wasn't this effort something your Center chose to become involved with?

Dr. Collins: Analysis of the mouse genome is an important component of the NCHGR's research mission. In the past year, one of the Human Genome Project's goals, the generation of a high resolution genetic linkage map of the mouse genome, was completed, largely through the efforts of a single NCHGR grantee. Completion of a physical map of the mouse genome is expected within the next two years. The NCHGR welcomed the participation of the Howard Hughes Medical Institute (HHMI) as an indication that this important private foundation recognizes the importance that detailed understanding of the mouse genome will have for progress in biomedical research. NCHGR also welcomed the opportunity to act as a partner with HHMI in the mouse gene identification project. The Center was involved in discussions with HHMI during the planning of project. NCHGR directly contributes to the project by providing support to investigators at Columbia University and at Wayne State University for production of the mouse cDNA libraries--collections of cloned DNA sequences that represent mouse genes. The HHMI funds go to support the efforts of the Washington University Sequencing Center-- which is primarily supported by NCHGR funds--to determine the actual DNA sequence of thousands of these cDNA clones. Further indication of the importance of this project was the contribution of a small amount of additional funds, for equipment purchases, by the NIH Director, from the Director's Discretionary Fund. This was an excellent example of partnership between publicly and privately funded genome research.

SIMILAR GENOME PROJECTS

Mr. Porter: Are other private groups funding similar genome projects?

Dr. Collins: The Human Genome Project's success in pursuing its goal of developing improved technology for genomic analysis has vastly increased the capability of many scientists, including those funded by NCHGR but also those supported by other organizations, both federal and private, to carry out highly sophisticated genetic research. For example, the complete genomic DNA sequences of several bacteria have been determined in work supported by at least three private concerns--as well as the Department of Energy, outside of its human genome program. Similarly, at least one plant genome is being pursued by a private seed company and several other plant genomes are the focus of a Department of Agriculture program.

There are also several examples of the ways in which private enterprise is contributing to the enrichment of the basic product of the Human Genome Project. Two years ago, Merck & Co. contributed several million dollars to support a large-scale cDNA sequencing effort at Washington University in St. Louis. This program has been remarkably successful, having met its goal of putting more than 400,000 partial cDNA sequences into the public domain; the success of the program has led to its continuation beyond its originally planned term. The value of these partial cDNA sequences is significantly increased by mapping them because that effectively maps the gene from which each is derived. The mapping efforts of the NCHGR-supported Genome Centers at Whitehead/MIT and Stanford have recently been supplemented by private contributions, from Sandoz and from The Institute for Genomic Research. These new private funds are being used to supply oligonucleotide primers, provided by two other companies, Research Genetics and Perkin-Elmer, to the mapping projects.

Finally, several private companies have been established to apply the new tools and capabilities provided by genomics research to the development of new medical and agricultural products. Similarly, several well-established large pharmaceutical and agricultural supply companies have rapidly incorporated genomics into their research and development programs. It has been estimated that over \$800,000,000 has been invested in genomic research by private companies.

LARGE-SCALE SEQUENCING OF HUMAN DNA

Mr. Bonilla: Dr. Collins, I hear that you have just made some grant awards to start human DNA sequencing on a pilot scale. How confident are you that the capability is there to complete the sequence of the human genome by the year 2005 as stated in your plan for the Human Genome Project?

Dr. Collins: I am pleased to say that scientists are now confident that, given sufficient resources, the human genome can be sequenced by 2005. The six pilot projects we funded are intended to test different approaches to scaling up DNA sequencing systems to the point at which the complete sequence of human DNA can be determined on the time scale planned for the Human Genome Project. In the course of the pilot program, over the next two years, we anticipate that approximately 100,000,000 base pairs of human DNA, or approximately 3 percent of the human genome, will be determined. We anticipate that these projects will implement more efficient strategies and improved technology which will further increase the output and further reduce the costs of large-scale sequencing laboratories.

Theoretically, even without such improvements, current sequencing technology could be sufficiently scaled up to sequence the human genome in the next 10 years. However, current sequencing costs are \$0.50 to \$0.75 per base pair in genome sequencing centers. Although this is an enormous improvement compared to the cost when we started, about \$10 a base pair, substantial reductions in the per base cost are still desirable before true large-scale sequencing is begun. Every one cent reduction in the per base cost represents an overall reduction of \$30 million in the total cost of sequencing the human genome. Reducing the cost to \$0.10 per base pair, which some of the pilot projects expect to achieve over the next three years, would be sufficient for the NCHGR, the DOE, and our international partners to fully scale up to sequence the entire genome by 2005.

PREVENTION AND TREATMENT OF HUMAN DISEASE

Mr. Bonilla: What has been the impact of the Human Genome Project on our ability to prevent and treat human disease? What can we look forward to in future in this regard?

Dr. Collins: The information and technology that have been produced by the Human Genome Project so far have already significantly improved the ability of biomedical research scientists to analyze the molecular basis of human disease. The vastly improved genetic linkage maps, physical maps, and DNA sequencing technology generated by the Human Genome Project have led to the isolation of the increasingly large numbers of human disease genes we have seen over the past few years.

Gene isolation is important because it allows investigators to understand, at a fundamental molecular level, how a mutation in a gene causes a human health problem. As a result of such understanding, scientists can design therapeutic and

preventative approaches in an informed, directed manner rather than relying on guesswork as in the past. An example of the power of this approach is the case of cystic fibrosis. In just a few short years after the isolation of the responsible gene, a number of new drugs are being developed in the laboratory and gene therapy clinical trials are underway.

We can expect new tools and information to continue to emerge from the HGP at an ever-increasing rate. This will translate into new therapies and preventative strategies at a similarly rapid rate. These tools will be particularly important in the analysis of complex diseases, those that involve several, or even many, genes as well as environmental components. Not only will improved genetic analysis allow the identification of the genes involved in such diseases as diabetes, heart disease, asthma, and psychiatric illness, but by allowing a clearer definition of the genetic and the environmental components of those conditions, will allow the development of more directed, more effective intervention strategies.

GENE IDENTIFICATION

Mr. Dickey: National Cancer Institute scientist Dean Hamer has conducted two studies in an attempt to find evidence for a "gay gene." It is my understanding that he is now under investigation for fraud in the first of the two studies. The *Chicago Tribune* reported on June 25, 1995, that a member of Hamer's research team accused Hamer of data manipulation in the first study. And, as for the second study, a fellow member of Hamer's research team said, "If the second study were the first study, it wouldn't have been published. The second study is not strong enough (statistically) to stand on its own." Please tell me what NCHGR's position is on Hamer's work?

Dr. Collins: The NCHGR does not have an official position on Dr. Hamer's work. His studies are preliminary and are undergoing the scrutiny that all research must undergo, that is, careful evaluation of the data and their interpretation followed by attempts by other researchers in other laboratories to replicate the findings or refute them.

The accusation of fraud is one that is being handled by the appropriate agencies with the Department of Health and Human Services.

Mr. Dickey: Please explain to me what you have learned about an "epilepsy gene" and what this will mean for epilepsy patients.

Dr. Collins: In March 1996, Pennacchio et al (*Science*, vol. 271, pp. 1731-1734) reported the identification of mutations in a gene called cystatin B in individuals with a rare, hereditary form of epilepsy called progressive myoclonus epilepsy (EPM1).

Cystatin B is a member of a large family of proteins normally made in the body and placed into body fluids, including the cerebrospinal fluid that bathes the brain. Cystatins act as inhibitors of other normally occurring enzymes, called proteases, that degrade and destroy proteins. The cystatins serve as a protective mechanism to make sure that the degradative proteases, which are needed to help recycle old and non-functional proteins in the cell, do not get out of hand and start degrading normally functioning proteins.

Epilepsy results from a large number of different kinds of injuries to the brain. The importance of the work of Pennacchio and colleagues is that it identifies a biochemical cause for the damage resulting in this form of epilepsy. By determining how a defect in this protein causes damage, we will gain a better understanding of this form of epilepsy and perhaps shed some light on the causes of other forms of epilepsy. Finally, it may be possible to design drugs that mimic the action of cystatin B and provide these as medications to replace the function of this protease inhibitor to children who have this form of epilepsy.

RESEARCH AND ETHICAL ISSUES

Mr. Stokes: What progress do you have to report since you were here last with respect to the Center's participation in helping to make sure that the ethical issues associated with human genome research are addressed?

Dr. Collins: The NCHGR has identified four priority areas among the ethical, legal, and social issues (ELSI) arising from human genome research: privacy and fairness in the use and interpretation of genetic information; responsible clinical integration of new genetic technologies; study and resolution of issues surrounding genetics research; and public and professional education about genetics and genetic technologies.

The NCHGR utilizes a multi-pronged approach to define, analyze, and address the ethical, legal, and social issues surrounding the Human Genome Project: the ELSI Branch; the Office of Policy Coordination; and the ELSI Working Group. The ELSI Branch, established in 1990, oversees a grant and contract portfolio of ELSI research, which has generated a substantive body of scholarship that informs policy development and implementation. The Office of Policy Coordination, established in 1995, is responsible for coordinating program planning, communications, legislative and policy development activities, which include issues related to the ethical, legal, and social implications of human genome research, and supports the activities of the ELSI Working Group. The ELSI Working Group, established in 1989, facilitates policy discussions and develops options and recommendations for addressing the ethical, legal, and social implications of human genome research. The newly formed intramural Genome Ethics Office will provide advice to the intramural research program. Together, these components comprise the NCHGR ELSI Program.

The NCHGR ELSI Program is committed to the study and analysis of issues related to the four priority areas and actively monitors progress in these areas to ensure that the issues raised by human genetics research are being identified and addressed.

I am pleased to have this opportunity to provide you with an update of the activities in each of the four priority areas.

I. Privacy and fairness in the use and interpretation of genetic information

In July 1995, the ELSI Working Group and the National Action Plan on Breast Cancer, a public-private partnership to address the research, education, and policy issues in breast cancer, jointly addressed the issue of genetic discrimination in health insurance and developed a set of four recommendations for state and federal policy makers:

- 1) Insurance providers should be prohibited from using genetic information, or an individual's request for genetic services, to deny or limit any coverage or establish eligibility, continuation, enrollment, or contribution requirements.
- 2) Insurance providers should be prohibited from establishing differential rates or premium payments based on genetic information or an individual's request for genetic services.
- 3) Insurance providers should be prohibited from requesting or requiring collection or disclosure of genetic information.
- 4) Insurance providers and other holders of genetic information should be prohibited from releasing genetic information without prior written authorization of the individual. Written authorization should be required for each disclosure and include to whom the disclosure would be made.

Since publication of these recommendations in *Science* in October 1995, several bills have been introduced in state legislatures and the U.S. Congress to address the issue of genetic discrimination in health insurance. Genetic information has been included in both the U.S. House and U.S. Senate health insurance reform bills among the factors that insurers may not use to deny or limit health insurance coverage.

In March 1995, the Equal Employment Opportunity Commission (EEOC) issued guidance that clarifies that protection under the Americans with Disabilities Act extends to individuals who may be discriminated against in employment decisions based on genetic information. The National Action Plan on Breast Cancer and the ELSI Working Group are initiating an analysis of the extent of protection provided by the EEOC guidance and will make policy recommendations where needed for additional protections.

II. Clinical integration of new genetic technologies

The ELSI Branch has focused much of its effort on basic and applied research projects to examine the impact of integrating new genetic technologies into health care practice, to establish a better understanding of the current state of knowledge by health professionals, and to develop recommendations about how to improve knowledge and incorporate these technologies into health care practice.

In 1994, the NCHGR (ELSI Branch), in collaboration with the National Cancer Institute, the National Institute of Mental Health, and the National Institute of Nursing Research, funded eleven, three-year research projects to examine issues surrounding testing and counseling for heritable breast, ovarian, and colon cancer risks. Known as the Cancer Genetics Studies Consortium, this effort is examining the psychosocial and clinical impact of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer to identify those

individuals who have an increased risk of developing cancer and those who do not. Knowledge and attitudes about genetic testing for cancer risks are being assessed and information is being gathered to establish clinical protocols for the optimum use of these risk assessment technologies. In the first year and a half of these projects, the investigators have carried out a comprehensive literature search and held extensive deliberations about follow-up recommendations for individuals found to have cancer predisposition gene mutations. The paper summarizing their findings will be submitted for publication this summer. The Consortium has also formed a task force on informed consent which will produce a model consent form for genetic testing for cancer risks by the end of 1996. Once completed, these projects will provide valuable experience-based guidance for genetic testing for cancer susceptibility genes.

The Task Force on Genetic Testing of the ELSI Working Group was established in 1995 to examine emerging issues surrounding the utilization and regulation of genetic tests. The goals of the Task Force are to: review the "state of the art" of genetic testing; examine the strengths and weaknesses of current practices and policies relating to testing; and, if needed, recommend changes or policy options that will ensure that only the appropriate tests are performed through qualified laboratories. The Task Force is chaired by Dr. Neil Holtzman, from Johns Hopkins University, and includes members from the biotechnology industry, professional societies, insurance industry, consumer organizations, and the ELSI Working Group. The liaisons from relevant federal agencies include AHCPR, CDC, FDA, HCFA, and HRSA. On March 15, 1996, a notice was published in the *Federal Register* announcing the availability of Interim Principles for public comment; written comments from the public will be accepted until May 31. At their April 29-30, 1996 meeting, the Task Force heard comments from the public on the Interim Principles, and will next consider formulation of recommendations and implementation strategies. The Task Force, which held their first meeting in April 1995, is expected to complete their work by late 1996.

III. Issues Surrounding Genetics Research

In response to concerns raised about the adequacy of informed consent and privacy protections when stored tissue samples are used in genetics research, the NCHGR and the Centers for Disease Control and Prevention supported a workshop to explore these issues. A paper that outlines the key issues and presents a series of recommendations resulting from this July 1994 workshop was published in the December 13, 1995 issue of the *Journal of the American Medical Association*, entitled "Informed Consent for Genetic Research on Stored Tissue Samples." The authors concluded that individuals should give informed consent before their identifiable stored tissues are used in genetics research.

In January 1996, the NCHGR and the Association of American Medical Colleges co-sponsored a meeting to explore ways to continue promising genetics research while appropriately addressing informed consent and privacy concerns. The participants, including members of several pathology associations, consumers,

members of the ELSI Working Group, representatives from the Office for Protection from Research Risks, and others concerned with these issues, viewed this meeting as an important first step in an ongoing dialog about this important issue. The NCHGR continues to work with professional and voluntary organizations, as well as ELSI researchers, on this important issue.

IV. Public and Professional Education

Most members of the general population and most health care professionals are not knowledgeable about genetics, genetic technologies and the possible ethical, legal, and social implications of having genetic information. It is critical that members of the public have an adequate understanding of the meaning of newly discovered genetic information. It is also essential that our nation's health care professionals have the knowledge, skills, and resources to effectively integrate this new knowledge and these new technologies into the diagnosis, prevention, and treatment of disease.

The ELSI Program has funded a number of educational projects for public education, K-12 education, education of policy makers and professional education. As a result of an evaluation of our education activities in 1995 the NCHGR has decided that the highest priority should be assigned to health care professional education in genetics at this time.

Efforts have been made to educate health care professionals in genetics, and many of these efforts have been effective. However, most genetics education activities for health professionals to date have been small in scale. These small-scale efforts now need to be coordinated with one another and supplemented by a national genetics education initiative. To this end, NCHGR has begun working with the American Medical Association and the American Nurses Association on a proposal to establish a National Coalition for Health Professional Education in Genetics. I will be pleased to keep the Committee informed about our progress in this area.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the center is doing to increase the number of African American and other minority research investigators involved in research under its purview?

Dr. Collins: The NCHGR has always emphasized research training as a means of recruiting new people into genomics research. Our focus for minorities has been to support individuals through the individual minority pre-doctoral fellowship program. Currently NCHGR supports 13 fellows in either the Ph.D. or combined MD/PhD program and a minimum of three new minority graduate students are selected for this 5-year fellowship each year.

The NCHGR Division of Intramural Research makes an active, vigorous effort to recruit, mentor and promote African-Americans and other minorities. Among our trainees and staff we have African-Americans, Hispanic Americans and other minority individuals at the faculty, post-doctoral and graduate student levels, in addition to trainees from Sub-Saharan Africa, North Africa, China, Japan, India, other Asian countries and Central/South America. Our faculty speak at HBCUs and at workshops and conferences designed to promote recruitment of minorities to the sciences.

The NCHGR's intramural program also offers long-term research training opportunities for minority scientists through its Visiting Investigator Program. We currently have one faculty member from an HBCU institution completing a one-year sabbatical. For faculty members who cannot take a sabbatical leave year to update their skills, the NCHGR offers support for individuals to take short-term courses. This year, we supported two faculty members to attend genome sciences courses at the Cold Spring Harbor Laboratory. Approximately ten faculty members participated in the Genomics Course for Faculty in Minority Institutions, which was held for the first time in the summer of 1995, and is being offered again in the summer of 1996.

The ELSI program is particularly interested in comparative ethnocultural issues as they relate to the impact of human genome research. One of the high priority areas for the ELSI program is clinical integration of new genetic technologies. The NCHGR, along with the NCI, NIMH, and NINR, funded the Cancer Genetics Studies Consortium (CGSC) to examine the impact of genetic testing and counseling for heritable breast, ovarian, and colon cancer risks. One important aspect of the projects is the examination of these issues within a variety of sociocultural contexts. A number of the projects are focusing on African-American, Hispanic and Native American populations.

Another high priority research area within the ELSI program is the use and interpretation of genetic information. The NCHGR has funded a number of projects that are designed to clarify these issues. One notable project is designed to identify the ethical, legal, and social implications of the Human Genome Project from the perspectives of two Native American communities, with particular emphasis on Native American concepts of privacy issues. This project will also describe the decision-making process in each community, with emphasis on collective decision-making and the extent of communal authority over individual members. These results will be shared throughout the project with the Native American populations and will be used to construct an approach to minority communities for ELSI research and for possible Human Genome Project research participation that will be more generally applicable, while still being culturally sensitive.

The NCHGR intramural program is also working on a project entitled West African Origins of Non-insulin Dependent Diabetes Mellitus (NIDDM) in African-Americans in collaboration with investigators from Howard University. The purpose of this project is to identify genes that carry susceptibility to NIDDM in

African-Americans. West African diabetologists will be encouraged to apply for support through a competitive research and development contract to carry out the field research for both a one year pilot study and a subsequent two year full scale study. A full time study coordinator from Howard University will train West African team members in use of standardized criteria appropriate to the region for the diagnosis of NIDDM and to ascertain relevant covariate information. Field staff will also be trained to administer a questionnaire to collect information on family history, diet and other risk factors for NIDDM. Analysis of some data will be performed in West Africa, while other parts of the analysis will be performed jointly by NCHGR and Howard University. If results of the pilot test are positive, the full scale study will be implemented.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at the center? How much is included in the FY 1997 budget for the center's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994.

Dr. Collins: While public and professional education are both important, health professional education is currently NCHGR's highest education priority. New information generated by the Human Genome Project and human genetic research is changing biomedical research and the practice of medicine. Health care providers will be the principal source of patient information as genetic tests and technologies move into mainstream medicine. Health care providers will be responsible for providing information about the appropriateness of genetic testing and interpretation of tests and test results. It is therefore essential that these health care professionals have the knowledge, skills, and resources to effectively integrate new genetic technologies into the diagnosis, prevention, and treatment of disease.

Efforts have been made to educate health care professionals in genetics. However, while these small-scale efforts have been effective, there is now a need for a coordinated national genetics education initiative. To this end, NCHGR is now working with the American Medical Association and the American Nurses Association on a proposal to establish a National Coalition for Health Professional Education in Genetics. The Coalition would be made up of senior representatives from health care professional organizations, government agencies including NCHGR, consumer and voluntary organizations, industry, and genetics professional organizations. Additionally, the NCHGR and HRSA have formed a workgroup to identify how these two organizations can collaborate in the area of health care professional education in genetics.

The NCHGR Office of Communications has developed a database of support groups and services for genetic and rare disorders in collaboration with the NIH Office of Rare Disease Research. The database currently contains information on 500 organizations and we are planning to expand it this year. It is part of the

Combined Health Information Database and will be accessible to the public on the NCHGR web site. Additionally, the NCHGR Office of Communications develops materials in a variety of formats including print, slides, and video, to convey the concepts of genetics and goals of the Human Genome Project to a general audience. A new video is currently being distributed to public schools nationwide.

The NCHGR ELSI Branch has funded over 20 education projects since its establishment. These include projects designed to educate health and other professionals about genetics and genetic technologies. For example, one education project assessed and analyzed knowledge, attitudes, experience, and practice of consumers and multi-disciplinary health professionals on issues related to the Human Genome Project. The investigators are now using this information to develop education programs. Another project will develop and field-test a semester-long high school course to be disseminated through a public broadcasting network using multiple telecommunications methods, including satellite, computer, audio, and print materials.

The FY 1997 budget request includes \$2,949,000, for outreach and public education. This compares to \$2,851,000 in FY 1996, \$2,287,000 in FY 1995, and \$1,708,000 in FY 1994.

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account, is this the case in your center? If so, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Collins: The NCHGR supports education through grants and contracts and the intramural research program, as well as in the research management and support activity. While some curtailing of educational activities funded by the research management and support budget was necessary, the funding of ELSI grants and intramural activities are not affected by this reduction.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between the center and the Office of Research on Minority Health? Are there specific projects in your center that are funded totally or partially by the office, explain?

Dr. Collins: The ORMH has been highly cooperative in helping us launch an initiative investigating diseases that affect African-Americans in disproportionate numbers. Last spring the ORMH provided major support for a workshop we held on the West African Origins of Non-Insulin Diabetes Mellitus (NIDDM) in African-Americans. The result of that workshop was a collaborative effort between the NCHGR and scientists at Howard University to write a proposal for a pilot study to investigate NIDDM in African-Americans. The ORMH has agreed to support the major portion of that pilot study; the NCHGR will support the genotyping aspects.

A second project, which is currently under discussion with the ORMH, involves a search for genes contributing to prostate cancer in African-Americans. If this project is approved by the ORMH it will be done in collaboration with an HBCU as part of a partnership program.

The ORMH has also provided funds to NCHGR to support a short course in modern molecular biology techniques. The NCHGR staff in collaboration with the National Institute of Neurological Disorders and Stroke developed the course which provided not only lectures but also laboratory exercises for minority students and faculty. NCHGR intramural staff were faculty members.

Mr. Stokes: To what extent are the nation's historically black colleges and universities participating in the research activities under the purview of the center?

Dr. Collins: Advances in genome research will depend upon a cadre of trained scientists and scholars who, in the short-term, will develop new and cost-effective solutions for the problems of large-scale mapping and sequencing and, in the long-term, will apply these technologies to biomedical research questions. To ensure that scientists and students in HBCU institutions are equipped to meet the new challenges of genome research successfully, the NCHGR has focused its resources on training opportunities for individuals at HBCU institutions, rather than direct support of HBCU institutions. In fiscal year 1995, the NCHGR supported several training activities for students and faculty. For example, two faculty members from HBCU institutions attended training courses in genomic technology at Cold Spring Harbor Laboratory. This activity was supported under the Minority Institution Travel Award Program. Five faculty members from HBCU institutions attended a two-week Genomics Course for faculty in minority institutions held in Bethesda at the NCHGR's intramural program. One faculty member from an HBCU institution is participating in the NCHGR's intramural Visiting Investigator Program working in the area of breast cancer research.

In fiscal year 1996, the NCHGR plans to continue and expand the training activities for students and faculty at minority institutions interested in pursuing a career in genomic sciences. The activities planned for FY 1996 are: 1) support of graduate and postdoctoral students and faculty members to attend workshops, courses and professional meetings under the Minority Institution Travel Award Program; 2) support HBCU faculty members to participate in the NCHGR's intramural Visiting Investigator Program; 3) support for a 2 week Genomics Course for faculty from minority institutions which include HBCUs; and 4) support for pre-doctoral students in HBCU institutions to pursue doctoral research in genomic analysis or related biomedical research areas.

GENE REPOSITORY - (RESOURCE OF CELL LINES)

Mr. Stokes: What is the association between genetic predisposition and the diseases and disorders?

Dr. Collins: The relationship between genetic predisposition and disease is like the relationship between potential and actual illness. A person has a disease or condition only when he or she actually manifests the symptoms or characteristics of that condition. On the other hand, a person can have a genetic predisposition to a disease, yet not display any evidence at all that the condition has manifested itself. For example, in the case of the breast cancer gene, BRCA1, a woman who has a mutation in the BRCA1 gene and has a family history of breast cancer has an 85 percent chance of getting breast cancer at some time in the future. However, she also has a 15 percent chance of never getting breast cancer. Whether the disease actually develops, i.e., symptoms appear, can depend on many factors, such as other genes and environmental or lifestyle conditions. Even in situations in which a mutation confers a 100 percent probability that the disease will develop, such as in Huntington's Disease, a person can live many productive years with a genetic predisposition prior to the onset of symptoms.

Mr. Stokes: What can you tell us about the status of the gene repository as it relates to the three leading causes of death?

Dr. Collins: The three leading causes of death in adults over age 25 are heart disease, cancer, and stroke. Most of these diseases have several contributing components including genetics, diet, and lifestyle. In order to study the contributions of the genetic component to these diseases, one must first identify families that have several generations of affected family members. The main objective of a proposed study that one HBCU was planning to pursue was a collection of blood samples from minority families from the general population without a focus on any specific disease. However, the grant application to actually develop the resource has not been submitted to the NIH for consideration.

Mr. Stokes: What is the status of the gene repository as it relates to African Americans, and other minorities?

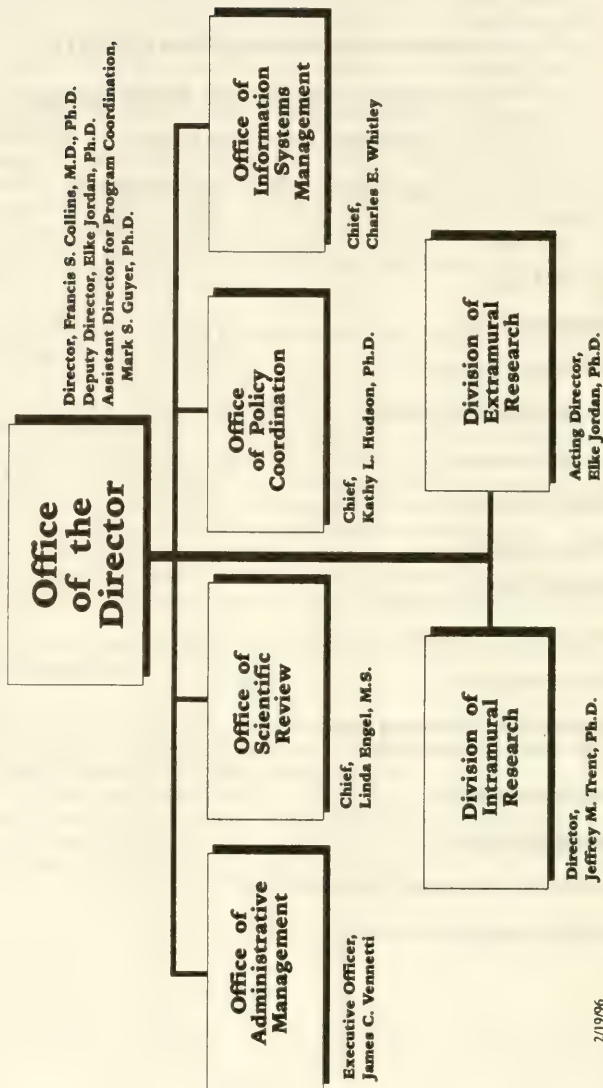
Dr. Collins: The NCHGR awarded a planning grant to an HBCU to develop a reference resource using DNA samples from African American families. This resource would be complementary to a similar resource of DNA samples from Caucasians, which has been used internationally to develop a genetic map of the human genome and to help in the isolation of specific genes that cause or contribute to various genetic and common diseases. The grant application to actually develop the resource has not been submitted to the NIH for consideration.

JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Center for Human Genome Research

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NATIONAL CENTER FOR HUMAN GENOME RESEARCH

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to human genome research, \$177,788,000.

Note—A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

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NATIONAL INSTITUTES OF HEALTH
National Center For Human Genome Research

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$152,010,000	\$170,041,000	\$177,788,000
Reduction in accordance with P.L. 103-333.....	-161,000		
Rescission in accordance with P.L. 104-19.....	-331,000		
Subtotal, Adjusted Appropriation.....	151,518,000	170,041,000	177,788,000
Real transfer from: Other NIH Institutes through the the NIH Director's one percent transfer authority.....	1,371,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....		-1,000,000	
Comparative transfer from: Other NIH Institutes for Management Fund adjustment.....	17,000		
Subtotal, adjusted budget authority.....	152,906,000	169,041,000	177,788,000
Unobligated balance, lapsing	-93,000		
Total obligations.....	152,813,000	169,041,000	177,788,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1995—\$619,000; FY 1996—\$950,000; FY 1997—\$1,000,000.

Also excludes funding for HIV activities: FY 1995—\$993,000; FY 1997—\$2,087,000, included in Office of AIDS Research, NIH.

Note: Excludes \$6,000 in FY 1995 and \$4,500 in FY 1996 for royalties.

Justification

National Center for Human Genome Research

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
174	\$152,906,000	192	\$169,041,000	192	\$177,788,000	--	+\$8,747,000

General Statement

This document provides justification for the FY 1997 Non-AIDS activities of the National Center for Human Genome Research (NCHGR). Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

In October 1995 the Human Genome Project completed its fifth year with a record of excellent progress toward its goals. The first goal of the Human Genome Project, creating a detailed genetic map for the human genome, has been accomplished. Recently, a team of U.S. investigators published a physical map of the human genome composed of over 15,000 well-ordered markers; this represents a major milestone on the way to the next goal—a comprehensive physical map of the human genome. Though original projections were that this map would not be finished until the end of 1998, completion is now expected by early 1997. These accomplishments have set the stage for the project's ultimate goal, sequencing all the DNA in the human genome by the year 2005.

In 1996, the NCHGR has increased its investment in two areas of DNA sequencing research. Pilot projects were initiated to address and resolve issues that will be confronted in large-scale sequencing of human DNA. These pilot projects are expected to generate between 50 and 100 million base pairs of human DNA sequence by 1998 and, in doing so, develop the methods that will be used in the determination of the complete human DNA sequence. NCHGR has also increased its investment in the development of new technology for DNA sequencing, concentrating on miniaturization and automation of current techniques.

To assure that genome data is rapidly available to the community, NCHGR supports a number of databases. These databases contain mapping and other Human Genome Project data and are all freely available on-line, increasingly through the World-Wide Web. Together, these databases are accessed more than 150,000 times per week. As research efforts scale up, it will be important for the management and analysis of both map and sequence data to be thoroughly automated. In FY 1997, NCHGR will continue to support the development of novel and improved computational tools for data management and analysis.

To help ensure that our social environment is prepared to maximize the benefits of genome research, the Ethical, Legal, and Social Implications (ELSI) program supports grants in four high-priority areas. These are: issues surrounding genetics research, especially informed consent; clinical integration of new genetic technologies; privacy and fair use of genetic information; and professional and public education in genetics. In the past year, the ELSI program has supported studies of informed consent for genetic research and the use of stored DNA samples, and the impact on individuals of genetic testing and counseling for heritable breast, ovarian, and colon cancer risks. ELSI researchers are also collecting information about the values, beliefs and experiences regarding genetic privacy and access to health insurance from individuals and family members with genetic conditions. Such information will better position policy-makers to develop safeguards needed for protecting genetic information.

The ELSI Working Group, an ad hoc committee of the NCHGR Advisory Council, has continued its efforts to explore the fair use of genetic information and, in conjunction with the National Action Plan on Breast Cancer, has developed and published recommendations to protect the public from genetic discrimination by health insurers. In 1995 a Task Force on Genetic Testing was established to examine the strengths and weaknesses of current practices and policies relating to the development of safe and effective genetic tests, and the quality of laboratories providing the tests. The Task Force is expected to provide criteria and general principles that will apply to a wide range of genetic tests and, when needed, develop recommendations to implement these criteria and principles. It is anticipated that the work of the Task Force will encompass a two-year timeframe.

The results of a recent survey conducted by an NCHGR grantee revealed that while fewer than half of health professionals in university affiliated programs had taken a course in genetics, almost 100 percent of physicians and 74 to 91 percent of nurses were involved in the delivery of genetic services. Because of the critical need for improving the training of health care professionals in genetics, NCHGR has made this a high priority area for its ELSI activities.

The NCHGR Division of Intramural Research (DIR) has developed a cutting-edge program to translate the tools of the Human Genome Project into knowledge about human genetic disease. While studies of disorders that arise from errors in single genes are on-going, DIR scientists are now investigating new strategies to tease apart the complex genetic and environmental contributions to common disorders such as prostate cancer and diabetes. Improved diagnostics are being developed to detect chromosomal abnormalities that lead to reproductive and developmental problems as well as cancers.

DIR researchers have also established clinical and laboratory training programs in medical genetics, including curriculum development for genetic counselors, nurses, physicians, and other health professionals.

Other intramural researchers are developing and analyzing gene therapy techniques for the treatment of brain cancer as well as immune diseases, including AIDS. Safer, more efficient vectors are being developed to carry healthy genes into human cells, and the underlying mechanisms for several inherited disorders are being elucidated. Animal models that mimic

genetic human birth defects are being developed to aid in understanding causes and possible treatments of several disorders

The President's appropriation request of \$177,788,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Center for Human Genome Research for the past 5 years has been as follows:

<u>Year</u>	<u>Amount</u>	<u>FTE</u>
FY 1992	\$104,762,000	44
FY 1993	106,134,000	55
FY 1994	126,475,000	139
FY 1995	152,906,000	174
FY 1996	169,041,000	192

Purpose and Method of Operation

The NCHGR carries out its mission through the support of research project grants, research center grants, research career awards, other research grants, training grants and fellowships, and intra/inter-agency agreements within NIH and with other Federal agencies. In addition, the NCHGR supports an intramural research program which conducts research on genes and their function in disease and the eventual prevention, treatment, or cure of human diseases. The scientific and administrative management and other overhead items are funded through the research management and support budget mechanism.

Overall Budget Policy

The FY 1997 budget request for the National Center for Human Genome Research is \$177,788,000. This amount represents an increase of \$8,747,000 or 5.17 percent over the FY 1996 estimate. This budget includes specific increases for NIH special emphasis areas. The largest increase (\$5,500,000) was provided for genetic medicine and NCHGR will be working closely with other NIH institutes and centers on this initiative. Other, smaller increases have been provided for new approaches to pathogenesis (\$500,000) and new preventive strategies against disease (\$1,000,000).

The funds requested for the above initiatives will be used to support additional research project grants and increases to current human genome research centers to make maps and develop the methods and technology needed to help scientists find the genes for the various diseases more rapidly. Within the Division of Intramural Research, investigators will be developing new approaches to understanding genetic diseases or those with a genetic component.

In the FY 1997 President's Budget Request, the NCHGR support for research project grants (RPGs) would increase by 7.65 percent over FY 1996. NIH plans to revise increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997

noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 68 competing RPGs, an increase of 19 competing RPGs over FY 1996, and 154 total RPGs, an increase of 13 total RPGs over FY 1996.

The FY 1997 budget request for research centers is \$41,996,000, a 7.03 percent increase over FY 1996. The FY 1997 budget request for other research grants is \$2,707,000, an increase of \$59,000, or 2.2 percent, over FY 1996 for the same number of awards. The FY 1997 budget requests \$3,209,000 for research training, an increase of \$10,000, or .31 percent. This increase provides for a 2.2 percent stipend increase for 107 full-time trainee positions, 4 fewer than FY 1996. For research and development contracts and inter-agency agreements, the request is \$3,140,000, a decrease of \$190,000, or -5.71 percent, for 8 awards, as compared to \$3,330,000 for 10 awards in FY 1996.

The FY 1997 budget request includes \$41,632,000 for the Division of Intramural Research. This is an increase of \$480,000, or 1.17 percent, over the FY 1996 estimate.

The FY 1997 budget request provides \$5,887,000 for research management and support activities, the same as the FY 1996 estimate.

Extramural Research

Authorizing Legislation-Section 301 and 487 of the Public Health Service Act.

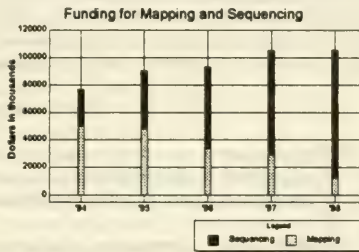
1997 Authorization: Indefinite.

Budget Authority:

<u>FY 1995</u>	<u>FY 1996</u>	<u>FY 1997</u>	<u>Increase</u> <u>or</u> <u>Decrease</u>
<u>Actual</u>	<u>Estimate</u>	<u>Estimate</u>	
\$107,473,000	\$122,002,000	\$130,269,000	+\$8,267,000

The goals of the Human Genome Project are to construct detailed genetic and physical maps of the human genome, to determine the complete nucleotide sequence of human DNA, to localize the estimated 50,000-100,000 genes within the human genome, and to analyze the genomes of several other organisms used extensively as model systems in research. October 1995, marked the fifth anniversary of the Human Genome Project, at which time we celebrated a record of outstanding progress toward our goals. As the mapping goals are achieved, the Human Genome Project will focus increased attention on DNA sequencing. This strategy is outlined in the NCHGR Budget Plan, FY 1994-1998, approved by the National Advisory Council for Human Genome Research in 1995.

Human Genome Project - NCHGR



Funding for the extramural program of the NCHGR for the last 5 years follows:

<u>Year</u>	<u>Amount</u>
FY 1992	\$99,836,000
FY 1993	100,517,000
FY 1994	101,470,000
FY 1995	107,473,000
FY 1996	122,002,000

Rationale for the budget request

The FY 1997 request is \$130,269,000 an increase of 6.78 percent over the FY 1996 estimate. Progress to date and future plans for achieving the next set of targeted goals are described below.

Mapping

Genetic Mapping. The first goal of the Human Genome Project, creating a detailed genetic map of the human genome, has been accomplished. This map is composed of more than 4,000 markers, which is 2-3 fold more detailed than was originally contemplated. The mouse genetic map, containing more than 7,000 markers, has also been completed. Development of these maps was made possible by advances in automation and sophisticated laboratory organization and information management techniques that now can be applied to other aspects of genome analysis. Indeed, these developments have already contributed to the success of large-scale physical mapping projects.

Physical Mapping. Recently, a team of U.S. investigators published a physical map of the human genome composed of over 15,000 well-ordered markers. This highly detailed and reliable physical map represents a major milestone on the way to the next goal--a comprehensive physical map of the human genome. Efforts to complete the physical map are on-going and the map is expected to be completed by early 1997. The completion of the genetic map, excellent progress toward completing the physical map, and advances in automation, informatics, and laboratory organization have set the stage for a focus on DNA sequencing.

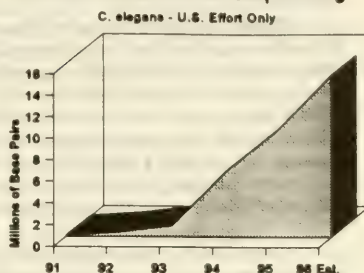
DNA Sequencing

Model Organisms are extremely valuable in the study of the human genome and genetics because of the significant similarity between human and non-human genomes, the relative ease of using model organisms in research, and the higher density of genes in non-human organisms.

International teams of researchers, using improved DNA sequencing technology, have made stunning advances toward the determination of the complete genomic sequences of the model organisms *Saccharomyces cerevisiae* (bakers' yeast) and *Caenorhabditis elegans* (a roundworm). Investigators from Europe, the United States, Canada, and Japan have now finished over 90 percent (11.3 million bases) of the *S. cerevisiae* genome and the complete sequence is expected by mid-1996. This will be the first complete DNA sequence of a complex, single-celled (eucaryotic) organism, a landmark achievement in biomedical science.

Significant progress is also being made on the next challenge, determining the genomic sequence of a multicellular organism. Collaborative teams from the United States and Great Britain have already completed more than 33 million bases of the 100 million-base genome of *C. elegans*; this represents the largest amount of known DNA sequence from any single organism. In 1996, the U.S. team is expected to produce 15 million bases of genomic DNA sequence; a 150-fold increase in sequence production since the team began this work in 1991. The *C. elegans* DNA sequence is expected to be complete by 1998.

Annual Rate of DNA Sequencing



New Opportunities. Sequencing technology has improved dramatically since the beginning of the Human Genome Project in 1990. However, there is still a need and opportunity for improving the technology to reduce costs and increase performance before the immense task of determining the sequence of the 3 billion base pairs of human DNA can be accomplished. In 1996, the NCHGR increased its investment in two areas of DNA sequencing research. Pilot projects for large-scale human DNA sequencing were initiated to address and resolve issues that will be confronted in large-scale sequencing of human DNA. These include how to convert the available physical map to a foundation for sequencing, how to sequence the large number and variety of repeated sequences that are prevalent in the human genome, and how to keep track of the enormous amounts of data that will be generated. These pilot projects are expected to produce 50 to 100 million base pairs of human DNA by 1998 and, in doing so, develop the methods to determine the complete human DNA sequence.

In 1996, the NCHGR also increased its investment in miniaturization of current sequencing methods and on automating and fully integrating those methods. Making sequencing reactions smaller speeds up the process and reduces the amounts of costly materials used, thus saving time and reducing cost. Automation reduces costs by decreasing the number of people required to run sequencing reactions. Not only will such improved technology make a significant contribution to the completion of the first human DNA sequence, it will be critical to interpreting the information contained in the DNA sequence. This investment promises to decrease costs and increase sequencing efficiency 100 to 1,000 times. The NCHGR will continue to support these areas as a priority in the coming year. Indeed, the improvement of sequencing technology and the sequencing of human DNA will become the major objectives of NCHGR in FY 1997. As mapping is completed, funds will be re-directed to sequencing.

Analysis of Genetic Disorders

Gene Identification. Along with determining the complete sequence of human DNA, one of the ultimate goals of the Human Genome Project is to identify all genes and other functional DNA elements. In parallel with the many efforts to identify particular disease genes, investigators are also engaged in efforts to identify genes in a wholesale fashion, rather than one by one. NCHGR has supported the development of both biological and computational gene-finding methods that will allow high-throughput, cost-effective gene identification and localization strategies. For example, a gene-finding technique termed direct cDNA selection (developed under NCHGR support) was recently used to isolate the major gene (located on chromosome 14) responsible for early-onset Alzheimer's Disease.

Two NCHGR-supported laboratories engaged in physical mapping of the human genome are placing large numbers of undefined gene fragments on their maps. These gene fragments are being generated rapidly by a privately funded project. The NCHGR effort will increase the usefulness of the fragments by showing their map locations and suggesting the location of the complete gene. In the past year, approximately 5,000 fragments have been mapped.

Complex Diseases. Most disease genes isolated so far cause "single gene" diseases, i.e. those in which a genetic change in just one gene results in a particular disease. In contrast, many common diseases (e.g., diabetes, cancer, asthma, Alzheimer's disease) are considerably more complex; they are termed "polygenic" or "multifactorial" because they involve several causative factors, both genetic and environmental. The genetic component itself may involve more than one gene while the relative contributions of the genetic and environmental factors may vary considerably. Analyzing complex diseases presents a significant challenge.

Improving our understanding of the underlying genetics of complex diseases will have a number of benefits. It will allow improved diagnosis and more effective treatments, which could be tailored specifically for an individual's genetic makeup. Finally, it will allow clearer distinctions to be made between genetic and environmental contributions, which could lead to better ways to address these major health problems by changing environmental influences.

The current high-resolution human genetic map has already allowed progress to be made in the analysis of complex diseases. Recently a British research group, using this map, suggested the involvement of as many as 19 genetic loci in type 1, or insulin-dependent, diabetes mellitus. However, technologies for finding genes involved in complex diseases are still far from ideal. Thus, in FY 1996 and FY 1997, some of the resources made available by successes in mapping are being redirected to develop markers that can be used in an automated fashion and better methods for large-scale genetic analysis.

Gene Function. Understanding the function of genes and other components of the human genome represents a major future challenge in biomedical research. One approach to gathering clues about gene function is finding sequence similarity (homology) between unknown genes and genes for which biological information is already known. The increasing availability of information about model organism genes is greatly facilitating the understanding of the function of

human genes. For example, the Alzheimer's disease gene described above has been found to be similar to a gene from the roundworm *Caenorhabditis elegans*. Although the exact function of the roundworm gene is not yet known, information is available about the physiological pathway in which it plays a role, providing a new clue for studies of Alzheimer's disease. In FY 1997, NCHGR plans to initiate more studies to develop comprehensive approaches to understanding the function of the human genome.

The Rat Genome Project. The study of many non-human organisms is important in understanding the genetics of human disease. For example, the rat is a widely-used model in the study of the genetic aspects of diseases such as hypertension, diabetes, cancer, and alcoholism. In light of the improvements in technology for genetic mapping, NCHGR collaborated with NHLBI and nine other NIH Institutes and Centers to develop and fund a "rat genome project." The successful collaboration of several NIH Institutes and Centers on the rat genome project can serve as a model for future collaborative efforts in genome research and its application to important human health problems.

Genome Informatics

Information management and analysis are essential to the success of the Human Genome Project. The experimental findings of the project must rapidly be made available through public databases and, in combination with improved methods of computational analyses, this will lead to a far more sophisticated understanding of human biology and disease.

Databases. In FY 1996 NCHGR supported a number of databases to meet the need for rapid and easy access to genome research data by researchers, clinicians, and the public. These databases contain mapping and other data from the Human Genome Project and are all freely available on-line, including through the World-Wide Web. They are all used extensively. In the aggregate, they are accessed more than 150,000 times per week.

Databases Supported by NCHGR

<u>Name of Database</u>	<u>Type of Database</u>	<u>World Wide Web Site</u>
GDB	human mapping data	http://gdbwww.gdb.org
MGD	mouse genome data	http://www.informatics.jax.org/mgd.html
Flybase	fruitfly genome data	http://morgan.harvard.edu
SGD	yeast genome data	http://genome-gopher.stanford.edu
GenLink	human linkage data	http://www.genlink.wustl.edu
OMIM	human genetic diseases	http://www3.ncbi.nlm.nih.gov/Omim/

These public databases strive to provide "consensus" or summary views of the genomes they represent, but they cannot collect the more detailed experimental data required by research scientists. Therefore, within the past two years, each of the Genome Science and Technology Centers supported by NCHGR has established a means of providing electronic access to their experimental results; this often includes the most recent data, which frequently are made available prior to publication. At present, the most popular form of electronic access is through individual

Genome Center Home Pages on the World-Wide Web; together, these home pages are now accessed more than 125,000 times per week. Through its support of the Genome Science and Technology Centers, NCHGR will continue to support the development of improved genome information resources in FY 1997.

Data Analysis. The second major area of emphasis for genome informatics is in analysis of data. In FY 1996, researchers supported by NCHGR released new and improved computer programs for constructing genome maps and for finding genes and other functional elements in DNA sequences. As Human Genome Project research efforts scale up, it will be important for the management and analysis of both map and sequence data to be thoroughly automated. In FY 1997, NCHGR will continue to support the development of novel and improved computational tools for data management and analysis within genome centers and in individual research laboratories.

Ethical, Legal, and Social Implications of Human Genome Research

High Priority Areas. The Ethical, Legal and Social Implications program supports research and education activities to anticipate, analyze and address the ethical, legal, and social issues that arise from the Human Genome Project. The ELSI priorities are: issues surrounding genetics research, including informed consent; clinical integration of new genetic technologies; privacy and fair use of genetic information; and professional and public education in genetics. In addition, the ELSI working group, an ad hoc committee of advisors, continues to anticipate and address the implications for individuals and society of new developments in human genetics.

Issues in Genetics Research. The NCHGR supports studies of informed consent for individuals participating in research and the role and responsibilities of Institutional Review Boards (IRB) in the review of genetic research protocols. The NCHGR, in collaboration with the National Centers for Disease Control and Prevention, sponsored an assessment of informed consent for genetic research using stored tissue samples. The resulting recommendations [*JAMA* 274,1786 (1995)] have elicited intensive discussion among researchers, health care providers, and IRBs and have heightened awareness of these important issues. In FY 1997, the NCHGR will continue to support research on informed consent and other issues to assure that individuals who choose to participate as research subjects are appropriately protected.

Clinical Integration of New Genetic Technology. NCHGR is supporting research to examine issues raised by the introduction of an increased amount of genetic information and technology into mainstream health care practice. During FY 1996, NCHGR, along with NCI, NIMH, and NINR continued support of research to examine the impact of genetic testing and counseling for heritable breast, ovarian, and colon cancer risks. The investigators of these projects, together with several others, have joined together to form the Cancer Genetics Studies Consortium (CGSC). This Consortium has examined informed consent and laboratory testing issues, developed a core set of questions to include in their assessments, and drafted recommendations for medical follow-up for individuals identified to be genetically predisposed to breast, ovarian, and colon cancer. One important aspect of these projects is the examination of these issues within a variety of sociocultural contexts. In FY 1996, the investigators will begin

testing individuals for mutations in the BRCA1 gene that predisposes individuals to breast cancer, and HNPCC a gene that predisposes individuals to colon cancer. Information from these projects will help guide the development of policies for genetic testing and counseling for inherited cancer risks.

In 1995, the ELSI Working Group established the Task Force on Genetic Testing. The Task Force is examining the strengths and weaknesses of current practices and policies relating to the development and delivery of safe and effective genetic tests, and the quality of laboratories providing the tests. The Task Force is developing criteria and principles applicable to a wide range of genetic tests and, when needed, will make recommendations for implementation of these principles. It is anticipated that the work of the Task Force will be completed early in 1997.

Privacy and Fair Use of Genetic Information. The ELSI program continues to support research and analysis of issues related to the privacy and confidentiality of genetic information including questions of ownership, control, disclosure and use of this information. Of particular concern is the fair use of genetic information in insurance, employment, education, adoption, and the criminal justice system. One such project will collect empiric information about the values, beliefs and experiences of individuals with genetic conditions and their families, regarding genetic privacy and access to health insurance. In addition, the ELSI Working Group, in conjunction with the National Action Plan on Breast Cancer, developed recommendations to protect the public from genetic discrimination by health insurers [*Science* 270,391 (1995)].

The NCHGR also funded research to identify the ethical, legal, and social implication of the Human Genome Project from the perspectives of Native American communities, with particular emphasis on Native American conceptions of privacy.

Public and Professional Education. The NCHGR has continued to support educational efforts aimed at improving public and health care professionals' understanding about genetic technologies and information. One group of investigators has gathered information about the level of knowledge of health professionals in university affiliated programs regarding genetics topics. The investigators found that while the health professional's formal education in genetics was extremely limited (fewer than half had taken even one formal course), their involvement in the delivery of genetic services was frequent (96 to 100 percent of physicians and 74 to 91 percent of nurses). The results of this project echo what was found by a large NCHGR-funded survey of 1,000 practicing nurses, carried out by the American Nurses Association. The results of the survey revealed that 63 percent of practicing nurses felt that they were "inadequately" or "hardly at all" trained in genetics; fewer than 10 percent had taken a formal course in genetics. Almost 70 percent of the respondents thought a course in human genetics should be a requirement for a nursing degree and 80 percent of the respondents indicated a willingness to take a continuing education course in genetics. These findings emphasize the need for the NCHGR to address health professional education in genetics.

The NCHGR is exploring joint health professional educational efforts in genetics with the health professional organizations and other government agencies.

Training Genome Scientists

Career Development. The NCHGR offers a variety of opportunities to scientists and students who wish to learn more about genomic research. The career development program is designed to allow scientists skilled in other disciplines to obtain training in biology and to apply their resulting cross-disciplinary skills to problems in genome research. The scientists trained through this program are making important contributions to the genome research efforts, particularly in the areas of informatics and instrumentation.

Research Training. The materials and information generated by the Human Genome Project will be used to answer fundamental questions in biology, such as understanding development or disease processes. To increase the capabilities of the next generation of scientists to use this information to understand gene function, the NCHGR supports approximately 100 pre- and post-doctoral students. Thirteen of these are minority pre-doctoral students.

Outreach Efforts. The NCHGR also supports several outreach efforts to stimulate the introduction of new techniques to the larger scientific community. These include short courses in informatics, cloning technologies, advanced microscopy, and linkage analysis. Each course provides didactic work and practicums, as well as individualized assistance to participants in incorporating the techniques and new research strategies into their research program upon return to their own laboratories.

Intramural Research

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
116	\$39,019,000	131	\$41,152,000	131	\$41,632,000	---	+\$480,000

The Division of Intramural Research utilizes cutting-edge genome science to develop streamlined techniques to rapidly isolate and analyze disease-linked genes, generate improved methods to diagnose inherited and acquired genetic disease, and investigate strategies, such as gene therapy, to reduce the harmful effects on human health.

Funding for the intramural research activity follows:

Year	Amount	FTE
FY 1994	\$18,824,000	80
FY 1995	39,019,000	116
FY 1996	41,152,000	131

Rationale for the Budget Request

The FY 1997 request is \$41,632,000, an increase of \$480,000, or 1.17 percent, over the FY 1996 estimate of \$41,152,000. This increase includes funds for intramural investigators who will be developing new approaches to understanding genetic diseases or those with a genetic component. Additionally, funds have been added to support the NIH Inter-Institute Genetics Clinic. This activity was transferred from the NIH Clinical Center to NCHGR in FY 1994. A selected subset of the current and planned research activities in the Division of Intramural Research are identified below.

Basic Research on Gene Transfer

The Laboratory of Gene Transfer is focused on uncovering the genetic basis of disease and using that information to develop new DNA-based therapies. In collaboration with other groups, both within and outside of NIH, the laboratory is using positional cloning and novel gene-finding techniques to close in on the genes for familial Mediterranean fever, Niemann-Pick type C disease and multiple endocrine neoplasia Type I. The lab is also characterizing the function of a number of previously identified genes, including the breast cancer gene, BRCA1, the gene responsible for ataxia-telangiectasia (A-T), and the Huntington disease gene.

Complex Diseases. Identifying genes that play a role in predisposing individuals to more common diseases with complex genetics is an increasingly approachable goal because of the availability of genetic maps developed by the Human Genome Project. Many challenging projects are underway, including studies aimed at identifying the genetic basis of adult-onset diabetes (which affects 6.57 million Americans) and of prostate cancer (which affects 200,000 Americans). Genes appear to play a role in both conditions, but the exact locations of the contributing genes have not been determined.

Gene transfer vectors. The inherent flaws often found in gene transfer vectors may preclude their medical use. To help solve this problem, the laboratory is working on the construction of a new, self-replicating "human artificial chromosome" (HAC), which contains DNA information sufficient for replication inside a cell. Because HACs can accommodate a gene of unlimited size, full-length genes can be introduced intact. A HAC containing the cystic fibrosis gene and a marker gene has been successfully introduced into cultured cells in pilot experiments. Applications to gene therapy as well as basic cell biology and gene identification are under development.

Cancer Genetics

Investigators in the Laboratory of Cancer Genetics are identifying genes that are involved in cancer development. This knowledge has immediate application for improved diagnosis of cancer and cancer risk and holds promise for improved strategies for cancer prevention and treatment.

For malignant melanoma, the chromosomal changes that take place during cancer development are being characterized and correlated with clinical progression. A second project is identifying genes differentially expressed during the progression of melanoma, and a third project centers on using chromosome breakpoints in malignant melanoma cells as another tool to identify genes contributing to cancer development. Investigators are also searching for genes involved in sarcomas, breast, ovarian, and prostate cancer.

Diagnostic Development

Research in the Diagnostic Development Branch focuses on the causes of human chromosomal abnormalities involved in pregnancy loss, early infant mortality, growth and developmental delay, birth defects with no known cause, and various cancers. Translating the fundamental technological and biological discoveries of genomics research into clinically useful tools is particularly emphasized.

Abnormalities of human development. A number of disorders, including lissencephaly, Prader-Willi syndrome, and Angelman syndrome are being studied as models of mechanisms causing birth defects, mental retardation, and other abnormalities of human development. Significant advances in the past year include identification of two hotspots for chromosome breakage and development of an improved assay for diagnosis of many different forms of these diseases.

Improving diagnostic tools A variety of techniques are used to investigate chromosomal aberrations that occur during the development of solid tumors. An important new chromosomal abnormality associated with the transition from severe dysplasia to invasive cervical carcinoma in 90 percent of tumors has been identified. The translation of this important finding to clinical application will be a priority for the coming year. Other tumors are being studied in a similar manner, including astrocytomas, breast cancers, colorectal cancers, and lymphomas.

Genetic Disease Research

The Laboratory of Genetic Disease Research is engaged in mapping and isolating genes contributing to human disease and in studying mouse models to understand fundamental problems in genetics and development.

Other Disease Genes Located Investigators have determined the chromosomal locations of several disease genes, including cerebral cavernous angiomas, cystinosis, Ellis van Creveld syndrome, pyknodysostosis, and synpolydactyly. Efforts are underway to isolate the Wolfram syndrome susceptibility gene.

The Mouse Model System The Laboratory of Genetic Disease Research continues to exploit the powerful methods of mouse embryology to create animal models for human developmental diseases. The mouse is an excellent model system because the genetic constitution of early embryos can be altered in a controlled manner to allow careful study of the effect of such alterations on development and health. Mouse mutants that serve as models for human inherited disorders, including Hirschsprung disease, Waardenburg syndrome, piebaldism and melanoma, are being studied.

Medical Genetics

The Medical Genetics Branch performs research into the clinical and natural history of genetic disease. In addition to research, the branch has a strong educational and clinical service mandate. Education programs are under development or in place for genetic counselors, genetic nursing, and M.D. and Ph.D. fellows in medical genetics. Research is also conducted on how best to communicate genetic information to individuals and families at risk. Medical Genetics Branch staff participate actively in clinics run by several NIH institutes.

Disorders of Connective Tissues The laboratory focuses on hereditary disorders of connective tissue, including Marfan syndrome and a number of skeletal dysplasias. Although linkage studies suggest that more than 99 percent of Marfan syndrome is caused by a specific mutation, certain screening methods have been unable to detect this mutation; only 20-30 percent of mutations are found by these methods. Branch researchers are working on a new set of tools to improve detection of this mutation. The molecular genetics of achondroplasia and hypochondroplasia, two of the more common human skeletal dysplasias, is also being actively pursued. Researchers have discovered that two mutations seem to predominate among persons with hypochondroplasia.

In an effort to begin applying the knowledge gained in the study of monogenic disorders to more complex traits, collaborations are underway on a genetic epidemiologic study of facial clefts. The causes of facial clefting in a study of Maryland infants with birth defects have been analyzed, and a significant gene-environment interaction between the transforming growth factor- α gene and a history of maternal smoking during fetal development was found.

Genetic Counseling and Education. Three genetic counseling research projects are now underway in the Medical Genetics Branch. All three involve cancer genetics testing and evaluating the impact of education and counseling on the outcomes for patients based on the results of testing. Nursing education in genetics is also being addressed. Goals include encouraging the incorporation of human genetics into educational preparation for nurses and preparation of continuing educational offerings on genetics.

Gene Therapy

Immune System Function. The Clinical Gene Therapy Branch develops gene transfer strategies for the study and treatment of inherited and acquired diseases. The branch performed a landmark clinical trial to use gene therapy to treat patients with adenosine deaminase (ADA) deficiency. To date, the data collected on these patients show that the procedure is safe and that long-term expression of the transferred gene can be achieved. The results from this study have been published in *Science* 270,475 (1995).

Brain Cancer. The branch has extensively studied the mechanisms involved in the bystander effect of certain agents, such as ganciclovir, that, when they are chemically altered by a transgene, kill not only proliferating tumor cells that express the transgene, but also tumor cells that do not express this transgene. Compounds have been identified that will upregulate the bystander effect. Preclinical studies are underway to explore new systems with emphasis on ovarian, breast, uterine, carcinomas, malignant melanoma, prostate, and bladder cancer.

Future Plans. In addition to the above studies, the branch will explore the application of gene therapy to Wiskott-Aldrich (WAS) syndrome, X-linked severe combined immune deficiency (SCID), and hemophilia in FY 1997.

Outreach

Visiting Investigator Program. For established investigators, this program provides faculty an opportunity to come to the NCHGR intramural program to collaborate with scientists here and to learn new techniques. Up to five scientists per year can participate in this program. In 1996, one of the participating visiting scientists, a minority female, is collaborating with several intramural scientists on projects related to diabetes and breast cancer, diseases which disproportionately affect some minority populations.

Another outreach program assists local high school teachers in incorporating genomic sciences into their science curricula. Yet another provides summer opportunities, in the form of a two-week course in the NCHGR laboratories on the NIH campus, to faculty from approximately

12 minority institutions. During this course, the faculty obtain new information that can be incorporated into their undergraduate molecular biology teaching programs and are provided with the opportunity to learn new laboratory techniques. NCHGR has also collaborated with NINDS and the Office of Minority Health in supporting a similar summer course for faculty/student partners in minority institutions.

Research Management and Support

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
58	\$6,414,000	61	\$5,887,000	61	\$5,887,000	---	----

This Research Management and Support activity provides the staff and resources necessary to support the overall administration and coordination of the NCHGR. Staff included in the activity provide direction for scientific programs, evaluate research needs, develop program announcements, manage the review and award of grants and contract applications, and support and monitor funded research projects. Other principal functions under this activity include planning and policy development, communications, policy analysis related to ethical, legal and social implications of human genome research, financial management, human resource development, grants management, general administrative services, and information systems management.

Funding for the research management and support activity during the last five years has been as follows:

<u>Year</u>	<u>Amount</u>	<u>FTE</u>
FY 1992	\$4,926,000	44
FY 1993	5,617,000	52
FY 1994	6,181,000	59
FY 1995	6,414,000	58
FY 1996	5,887,000	61

Rationale for the Budget Request

The FY 1997 budget request for Research Management and Support is \$5,887,000 the same as the FY 1996 estimate.

These funds will be used to support the Office of the Director and the Division of Extramural Research. The Office of the Director sets policies and provides the guidance and professional leadership needed to manage the NCHGR. Within the Office of the Director are the various administrative and policy offices, which provide advice to the Director and NCHGR staff and direct the administrative and policy functions of the NCHGR; the Office of Scientific Review; and the Office of Information Systems Management. The Division of Extramural Research is responsible for the administration of the NCHGR portfolio of research grants, research training awards and collaborative activities.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Research grants:						
Research projects:						
Noncompeting.....	90	\$47,263,000	83	\$48,856,000	77	\$45,006,000
Admin. supplements.....	(10)	746,000	(4)	487,000	(4)	497,000
Competing:						
Renewal.....	6	2,200,000	8	3,816,000	11	5,367,000
New.....	29	10,086,000	41	17,867,000	57	\$25,127,000
Supplements.....	1	159,000	0	0	0	0
Subtotal, competing.....	36	12,445,000	49	21,683,000	68	30,494,000
Subtotal, res. proj.....	126	60,454,000	132	71,026,000	145	75,997,000
SBIR/STTR.....	13	2,180,000	9	2,560,000	9	3,220,000
Total, RPGs.....	139	62,634,000	141	73,586,000	154	79,217,000
Research centers:						
Specialized/comp. centers.....	15	37,996,000	14	39,239,000	14	41,996,000
Other research:						
Research career programs.....	13	980,000	12	935,000	12	956,000
Other research related.....	20	1,083,000	25	1,713,000	25	1,751,000
Subtotal, other research.....	33	2,063,000	37	2,648,000	37	2,707,000
Total, research grants.....	187	102,693,000	192	115,473,000	205	123,920,000

Training:

Individual awards:						
Noncompeting.....	18	504,000	19	550,000	22	662,000
Competing.....	13	332,000	7	203,000	0	0
Subtotal, individual.....	31	836,000	26	753,000	22	662,000
Institutional awards:						
Noncompeting.....	16	420,000	55	1,761,000	85	2,547,000
Competing.....	55	1,590,000	30	685,000	0	0
Subtotal, institutional.....	71	2,010,000	85	2,446,000	85	2,547,000
Total, training.....	102	2,846,000	111	3,199,000	107	3,209,000
Research and development						
contracts.....	8	1,934,000	10	3,330,000	8	3,140,000
Intramural.....						
	FTEs		FTEs		FTEs	
	116	39,019,000	131	41,152,000	131	41,632,000
Research management and						
support.....	58	6,414,000	61	5,887,000	61	5,887,000
Total.....						
	174	152,906,000	192	169,041,000	192	177,786,000

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Center for Human Genome Research

Budget Authority by Activity
(Dollars in thousands)

	1993 Actual		1994 Actual		1995 Actual		1996 Estimate		1997 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Human Genome Research...		\$100,517		\$101,470		\$107,473		\$122,002		\$130,269		+\$8,267
Intramural Research.....			80	18,763	116	38,926	131	41,152	131	41,632		+480
Research management and support.....	55	5,576	59	6,147	58	6,414	61	5,867	61	5,867		—
Total obligations.....	55	106,095	139	126,380	174	152,813	192	169,041	192	177,768		+8,747
Unobligated balance lapsing.....		39		95		93						
Total, budget authority....	55	106,134	139	126,475	174	152,906	192	169,041	192	177,768		+8,747

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Center for Human Genome Research

Summary of Changes

1996 Estimated budget authority.....	\$169,041,000
1997 Estimated budget authority.....	177,788,000
Net Change	+ 8,747,000

	1996 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
<u>Changes:</u>				
A. <u>Built-in:</u>				
1. Intramural Research				
a. Within grade increase.....		\$9,959,000		+\$123,000
b. Annualization of January 1996 pay raise.....		9,959,000		+50,000
c. Annualization of January 1996 locality pay.....		9,959,000		+13,000
d. January 1997 pay increase.....		9,959,000		+228,000
e. Increased cost of centrally furnished services.....		5,110,000		+153,000
f. Increased cost of service and supply fund.....		2,590,000		+57,000
g. Increased cost of supplies and materials.....		23,493,000		+517,000
Subtotal.....				+1,141,000
2. Research Management and Support				
a. Within grade increase.....		3,631,000		+64,000
b. Annualization of January 1996 pay raise.....		3,631,000		+18,000
c. Annualization of January 1996 locality pay.....		3,631,000		+5,000
d. January 1997 pay increase.....		3,631,000		+84,000
e. Federal employees comp- ensation fund.....				+2,000
f. Decreased cost of centrally furnished services.....		1,051,000		-47,000
g. Increased cost of service and supply fund.....		45,000		+1,000
h. Increased cost of supplies and materials.....		1,160,000		+26,000
Subtotal.....				+153,000

Summary of Changes (cont)

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.....	83	48,856,000	-8	-3,850,000
b. Admin supplements.....	(4)	487,000		+10,000
c. Competing.....	49	21,683,000	+19	+8,811,000
d. SBIR/STTR.....	9	2,560,000		+680,000
Total.....	141	73,586,000	+13	+5,631,000
2. Research centers.....	14	39,239		+2,757,000
3. Other research.....	37	2,848,000		+59,000
4. Research training.....	111	3,199,000	-4	+10,000
5. Research & dev contracts.....	10	3,330,000	-2	-190,000
6. Intramural:				
a. New approaches to pathogenesis program increase.....		41,152,000		+500,000
b. Program decrease.....		41,152,000		-1,161,000
7. Research management and support:				
a. Program decrease.....		5,887		-153,000
Subtotal.....				+7,453,000
Total changes.....				+8,747,000

NATIONAL INSTITUTES OF HEALTH
National Center for Human Genome Research

Budget Authority by Object

	<u>1996 Estimate</u>	<u>1997 Estimate</u>	<u>Increase or Decrease</u>
Total compensable work years:			
Full-time equivalent employment.....	192	192	—
Full-time equivalent of overtime and holiday hours.....	2	2	—
Average ES salary.....	\$113,597	\$116,890	+\$3,293
Average GMGS grade.....	10.3	10.3	—
Average GMGS salary.....	\$44,325	\$45,610	+\$1,285
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)...	\$43,292	\$44,487	+\$1,195
Average salary of ungraded positions....	\$23,878	\$24,356	+\$478
Personnel compensation:			
Full-time permanent.....	\$6,566,000	\$6,904,000	+\$338,000
Other than full-time permanent.....	2,088,000	2,200,000	+112,000
Other personnel compensation.....	289,000	304,000	+15,000
Special personnel service payments....	2,373,000	2,373,000	—
Subtotal, personnel compensation.....	11,316,000	11,781,000	+465,000
Personnel benefits.....	2,267,000	2,387,000	+120,000
Benefits for former personnel.....	7,000	7,000	—
Travel and transportation of persons....	510,000	503,000	-7,000
Transportation of things.....	167,000	163,000	-4,000
Rent, communications, and utilities.....	408,000	400,000	-8,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Printing and reproduction.....	169,000	165,000	-4,000
Other services:			
Consulting services.....	365,000	318,000	-47,000
Other services.....	7,967,000	7,928,000	-39,000
Purchases from government accounts...	9,626,000	9,544,000	-82,000
Operations and maintenance of facilities..	597,000	584,000	-13,000
R&D contracts.....	586,000	508,000	-78,000
Operations and maintenance of equipment..	180,000	173,000	-7,000
Supplies and materials.....	8,027,000	8,100,000	+73,000
Equipment.....	8,127,000	8,046,000	-81,000
Grants, subsidies & contributions.....	118,672,000	127,129,000	+8,457,000
Insurance claims and indemnities.....	42,000	44,000	+2,000
Interest and dividends.....	8,000	8,000	—
Total.....	169,041,000	177,788,000	+8,747,000

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Center for Human Genome Research

Administrative Costs

	1996 Current Estimate	1997 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1).....	\$6,566,000	\$6,904,000	+\$338,000
Other than Full-time permanent (11.3).....	2,088,000	2,200,000	+112,000
Other Personnel Compensation (11.5).....	289,000	304,000	+15,000
Special Personnel Service (11.8).....	2,373,000	2,373,000	—
Total Personnel Compensation (11.9)....	11,316,000	11,781,000	+465,000
Personnel Benefits (12.0).....	2,267,000	2,387,000	+120,000
Benefits for Former Personnel (13.0)....	7,000	7,000	—
Travel (21.0).....	510,000	503,000	-7,000
Transportation of Things (22.0).....	167,000	163,000	-4,000
Rental Payments to Others (23.2).....	5,000	5,000	—
Communications, Utilities, and Miscellaneous Charges (23.3).....	403,000	395,000	-8,000
Printing and Reproduction (24.0).....	169,000	165,000	-4,000
Consulting Services (25.1).....	365,000	318,000	-47,000
Other Services (25.2).....	7,967,000	7,928,000	-39,000
Purchase of goods and services from government accounts (25.3).....	9,626,000	9,544,000	-82,000
Operation and Maintenance of Facilities (25.4)...	597,000	584,000	-13,000
Operation and Maintenance of Equipment (25.7)...	180,000	173,000	-7,000
Supplies and materials (26.0).....	8,018,000	8,090,000	+72,000
Total.....	41,597,000	42,043,000	+446,000

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

SIGNIFICANT ITEM IN HOUSE APPROPRIATIONS COMMITTEE REPORT

1996 House Appropriations Committee Report LanguageItem

New strategies -- The Committee encourages NCHGR to take advantage of newly proposed strategies for sequencing the human genome that utilize the best available plans and technology and that may enable the Human Genome Project to complete the accurate sequencing of the human genome ahead of schedule and under budget.

Action Taken or to be Taken

Considerable progress has been made in the improvement of technology for DNA sequencing, and in the organizational and project management aspects of large-scale DNA sequencing projects. At the same time, the mapping goals of the Human Genome Project are approaching completion. In response to these advances, the focus of the NCHGR's research program is moving from mapping to DNA sequencing. A major step in this direction was a Request for Applications issued by the NCHGR to further stimulate the development of high-capacity DNA sequencing capability by initiating pilot projects for large-scale sequencing of human DNA. A considerable number of applications were received in response to this RFA. Awards will be made in the spring of 1996.

As efforts in sequencing human DNA are expanding in the U.S., projects to sequence human DNA are also being expanded in other countries, for example the U.K. and Germany, as befits the international nature of the Human Genome Project. There is considerable interest on the part of NCHGR and the funding sources in these other countries in coordinating the expanded sequencing projects. The purpose of such coordination is to ensure that overlap and duplication of effort is minimized and to encourage exchange of useful information among the researchers. The first international meeting of DNA sequencers was held in February 1996 to initiate this coordination.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Authorizing Legislation

<u>PHS Act/ Other Citation</u>	<u>U.S. Code Citation</u>	<u>1996 Amount Authorized</u>	<u>1996 Estimate</u>	<u>1997 Amount Authorized</u>	<u>1997 Estimate</u>
Research and Investigation...					
Section 301	42#241	Indefinite		Indefinite	\$174,579,000
National Center for Human Genome Research			\$165,842,000	Indefinite	
Section 485B	42#285g	Indefinite			
National Research Service Awards		Such sums as necessary	3,199,000	Authorizing legis- lation is pending	3,209,000
Total Budget Authority...			169,041,000		177,788,000

NATIONAL INSTITUTES OF HEALTH

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National Center for Human Genome Research

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation	1/
1990	\$100,000,000	\$62,000,000	— 2/	\$59,938,000	
1990 Sequester				-400,000	
1991	108,029,000	66,131,000	108,264,000	87,418,000	3/
1991 Sequester				-1,000	
1992	110,487,000	93,115,000	109,309,000	104,762,000	4/
1993	110,429,000	107,217,000	107,217,000	106,239,000	5/
1994	134,549,000	119,030,000	131,925,000	127,112,000	6/
1995 7/ 1995 Rescission	152,010,000	151,878,000	151,878,000	151,518,000	8/
				-331,000	
1996	166,678,000 7/	170,041,000	163,943,000 7/	170,041,000	
1997 7/	177,788,000				

1/ Reflects enacted supplements, rescission, and reappropriations.

2/ The Senate did not provide funds for the National Center for Human Genome Research; however, the Senate allowance included \$61,847,000 for the Human Genome Initiative within the National Institute of General Medical Sciences' account.

3/ Excludes enacted administrative reductions of \$2,313,000 and the enacted rescission of \$116,000.

4/ Excludes enacted administrative reductions of \$383,000.

5/ Excludes enacted administrative reductions of \$978,000.

6/ Excludes rescission of \$1,589,000.

7/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS research.

8/ Excludes enacted administrative reductions of \$161,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Detail of Full-Time Equivalent Employment

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director	6	6	6
Office of Admin. Management	22	22	22
Office of Policy Coordination	9	10	10
Office of Information Systems Management	3	4	4
Office of Scientific Review	6	6	6
Div. of Extramural Research	12	13	13
Div. of Intramural Research	116	131	131
Total	174	192	192

Average GS/GM Grade

1991.....	9.8
1992.....	10.1
1993.....	10.2
1994.....	10.3
1995.....	10.5
1996.....	10.3
1997.....	10.3

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
ES-6.....	3	3	3
ES-4.....	2	3	3
ES-3.....	1	1	1
Subtotal.....	6	7	7
GS/GM-15.....	12	12	12
GS/GM-14.....	11	12	12
GS/GM-13.....	17	17	17
GS-12.....	17	19	19
GS-11.....	27	27	27
GS-10.....	1	2	2
GS-09.....	12	15	15
GS-08.....	10	10	10
GS-07.....	14	16	16
GS-06.....	1	1	1
GS-05.....	3	4	4
GS-04.....	3	6	6
GS-02.....	4	4	4
GS-01.....	0	1	1
Subtotal.....	132	146	148
Grades established by Act of July 1, 1944 (42 U.S.C. 207);			
Director Grade.....	1	1	1
Senior Grade.....	2	2	2
Full Grade.....	2	3	3
Senior Assistant Grade.....	1	1	1
Subtotal.....	6	7	7
Ungraded.....	43	47	47
Total, permanent positions	160	160	160
Total positions, end of year	187	207	207
Total full-time equivalent employment, end-of-year	174	192	192
Average ES level.....	4.8	4.7	4.7
Average ES salary.....	\$110,583	\$113,597	\$116,890
Average GS/GM grade..	10.5	10.3	10.3
Average GS/GM salary..	\$43,149	\$ 44,325	\$ 45,610

TUESDAY, APRIL 23, 1996.

**NATIONAL INSTITUTE ON DEAFNESS AND OTHER
COMMUNICATION DISORDERS**

WITNESSES

DR. JAMES B. SNOW, JR., DIRECTOR, NIDCD

DR. HAROLD VARMUS, DIRECTOR, NIH

W. DAVID KERR, EXECUTIVE OFFICER, NIDCD

PATIENCE T. SPARKS, BUDGET OFFICER

**DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET,
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

MARK LANGER, SIGN LANGUAGE INTERPRETER

GARY MORIN, SIGN LANGUAGE INTERPRETER

Mr. PORTER. Our hearings continue with the National Institute on Deafness and Other Communication Disorders. We are pleased to welcome Dr. James Snow, the Director of the Institute. Dr. Snow, we appreciate your coming to testify today. If you would introduce the people who are with you and then proceed.

INTRODUCTION OF WITNESSES

Dr. SNOW. Thank you very much, Mr. Porter. To my left is Mr. W. David Kerr, the Executive Officer of the NIDCD, on my right is Ms. Patience T. Sparks, the Budget Officer of the NIDCD, Dr. Varmus you of course know, and Mr. Dennis Williams. I would especially like to introduce Mr. Mark Langer, the NIH sign language interpreter. He will be assisted a little later on by Mr. Gary Morin.

OPENING STATEMENT

Mr. Chairman, members of the subcommittee, I am pleased to tell you about the progress of the National Institute on Deafness and Other Communication Disorders. Today, 46 million Americans are experiencing the tough realities of living with communication disorders. Many of these disorders are present at birth, and most last a lifetime. All are either a continuing expense or a costly disability.

The NIDCD is in its eighth year, and I am pleased to report real progress in the diseases affecting hearing, balance, smell, taste, voice, speech, and language. These include the ordeals of aphasia and stuttering, the debilitating effects of balance disorders, the pain and expense of otitis media in infants and children, the effects of diminishing senses on older Americans leaving them vulnerable to loss of communication, falls, spoiled food, gas leaks, and poor nutrition, and the overwhelming distress of persistent noise in the ears in individuals with tinnitus. For all of these Americans, the progress cannot come quickly enough.

NIDCD scientists, for example, working with the mothers at the White Earth Reservation in Minnesota, are identifying risk factors for chronic otitis media. The NIDCD has focused intramural resources on vaccine development against otitis media. Although conjugate pneumococcal vaccines are in phase I and II clinical trials, the recalcitrant problem has been finding the right conjugated vaccine against the nontypable *Haemophilus influenzae*. Utilizing basic research on the outer membrane of the bacterium, NIDCD scientists have conjugated a derivative of the endotoxin with tetanustoxoid. This vaccine has caused a bactericidal immune response in two animal models. Based on this breakthrough, a clinical trial of the vaccine is now planned.

One in five hundred children have some form of autism. Autism is characterized by a language disorder, withdrawal, and extreme reactions to changes in the environment. Progress in autism is underway through an important collaboration between NIDCD intramural scientists and two extramural labs. An individual with autism was recently found to have a translocation at an unexpected gene site called GRP-R, the gastrin releasing peptide receptor, perhaps causing a loss of function of that gene. The association of the GRP-R gene with autism may be our first breakthrough in the molecular genetics of language.

Progress in the molecular genetics of hereditary hearing impairment and the sense of smell are accelerating. Only two genes responsible for hearing impairment were known when the NIDCD was established. Now, more than forty have been found. Molecular biology has allowed exploration of an enormous family of receptor genes that reside on the surface of the olfactory neurons in the nose. Quite amazingly, all the neurons expressing a given receptor subtype project their axons to just one or two discrete foci within the olfactory bulb. This organization has long eluded investigators approaching the problem through other techniques.

Within the hearing portfolio, research and development of multi-channel cochlear implants, improved speech processors, and more effective rehabilitative strategies have all been supported by the NIDCD. Additionally, a recent consensus development panel recommended the use of cochlear implants for an additional one million Americans who obtain marginal benefit from hearing aids.

For the parents of a child born deaf, whether those parents be hearing or deaf, the choices that must be made in order to ensure having both the ability to communicate freely and the ability to communicate within a hearing society are ongoing challenges. NIDCD research addresses these needs. In the study of language acquisition by deaf children, the NIDCD is supporting study of the critical period for language acquisition, focusing on learning American sign language and written English by deaf children, and the effect of early bilingualism.

Using powerful imaging equipment available in the Clinical Research Center, scientists are demonstrating that cerebral function associated with language may be fundamentally different in persons who stutter. Stuttering interferes with social development, employment, and communication. Scientists in the Neuroimaging Unit have found that persons who stutter differ markedly in the way in which they formulate and express language. Instead of the

typical left hemisphere dominance seen in control subjects, brain activity in individuals who stutter is bilateral or predominantly in the right hemisphere. This line of investigation is giving us new information on the mechanisms that control speech and language.

In a major initiative in clinical research, NIDCD is making a five-year commitment to the conduct of clinical trials through the support of cooperative groups. These groups of fifteen to twenty facilities with research capabilities and experience are poised to answer priority questions. The trials will address efficacy of a wide range of therapy in the mission areas of the NIDCD and accelerate our ability to deliver research results to the people as quickly as possible. The NIDCD staff are grateful for the support that NIDCD has received and are proud of the research that it has been able to foster.

The fiscal year 1997 budget request is \$179,090,000. Thank you for your consideration. I will be happy to answer questions.

[The prepared statement of Dr. James Snow follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

National Institute on Deafness and Other Communication Disorders

Mr. Chairman, Members of the Subcommittee, I am grateful for this opportunity to tell you about the progress of the National Institute on Deafness and Other Communication Disorders (NIDCD).

Today 46 million Americans are experiencing the tough realities of living with communication disorders. Many of these disorders are present at birth, and most last a lifetime. All are either a continuing expense or a costly disability. For individuals who have a balance problem, walking, let alone working, is an ordeal. For individuals whose spinning sensation is not even relieved by lying down, the progress cannot come fast enough. For the parents of a child born deaf, whether those parents be hearing or deaf, the choices that must be made in order to ensure having both the ability to communicate freely and the ability to communicate within a hearing society are ongoing challenges. For older persons whose senses are diminishing, for whom hearing problems are causing loss of communication with family and friends, for whom lessened sensitivity to smell makes them vulnerable to gas leaks in the home, and for whom loss of the sense of taste leaves them subject to poor nutritional status, the progress cannot come fast enough. For the aphasic individual, struggling to understand and to be understood and for the child who stutters in class and also struggles to be understood, the progress can't come fast enough. For the millions of children who are taken in pain to emergency rooms and physicians' offices for recurrent bouts of otitis media, still the reason for the most visits to emergency rooms and physicians' offices and the leading indication for prescribing antibiotics for children in the United States, and for their sleepless parents who must decide to miss work to take them for help, the progress can't come quickly enough.

The NIDCD is in its eighth year, and I am pleased to report real progress in the search for solutions to these problems. The NIDCD has focused its intramural resources on the development of a vaccine against otitis media. Two principal bacteria cause otitis media: *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae* (NTHi). Unfortunately, antibiotic-resistant forms of both are being encountered more frequently.

For a vaccine to be protective, the immune system must make antibodies against it. To prevent infection, antibodies must attach to bacteria and kill them. In the case of otitis media, immunity must be achieved in the first few months of the child's life just as is the case with Hib vaccine against meningitis. The strategy for achieving early immunity is to create a conjugated vaccine. Conjugated pneumococcal vaccines are in phase 1 and phase 2 clinical trials. The recalcitrant problem has been finding the right conjugated vaccine candidate for NTHi. Utilizing basic research on the outer membrane of the NTHi, NIDCD scientists have used oligosaccharide derived from the lipooligosaccharide (LOS) or endotoxin. They have developed an elegant

method of removing the fatty acid from the lipid, detoxifying it. The vaccine unit at NIDCD has conjugated the detoxified LOS with the protein of tetanus toxoid. This forms a vaccine which induces a bactericidal immune response in two different animal models. Based on this breakthrough, a phase I clinical trial of the vaccine is now planned.

The permanent damage to the middle ear caused by otitis media is referred to as chronic otitis media. Native Americans have a higher prevalence of chronic otitis media than does the general population. Working with mothers at the White Earth Reservation in Minnesota, NIDCD scientists are identifying risk factors for chronic otitis media.

NIDCD's multi-faceted approach to otitis media illustrates the coordination of efforts and blend of opportunities that will yield essential information about a vaccine and its appropriate use, while pursuing knowledge about diverse populations for whom it will be beneficial.

Similarly, the integration of knowledge and careful collaboration between the NIDCD intramural program and the extramural scientific community is yielding an important breakthrough in autism. Autism is the lifelong, neurogenic communication disorder that usually is apparent in children by 30 months of age. It is characterized by a language disorder, withdrawal and extreme reactions to changes in the environment. Autism occurs four times more frequently in boys. For every 10,000 children, five have the fully expressed disorder and another fifteen have two of the cardinal features. More than 4,000 American families have two or more autistic children. Recently, an individual with autism was found to have a translocation at the gastrin releasing peptide receptor (GRP-R) gene, perhaps causing a loss of function of that gene. The association of the GRP-R gene with autism may be our long awaited first breakthrough in the molecular genetics of language. The NIDCD intramural lab is collaborating with two extramural research centers to expedite analysis of DNA samples from a large number of individuals with autism. Initial findings indicate that GRP-R mutations are frequent in autistic individuals. These studies may reveal abnormalities in neurotransmitter and/or neuropeptide systems that may be a part of the pathophysiology of autism and may be amenable to substitution therapy.

Language has been the last of the communication disorders to yield to molecular investigation, and this breakthrough promises a cascade of new opportunities that will validate a long range planning effort undertaken by NIDCD: Last year, I told the Committee that we were convening the Integrated Policy and Planning Working Group to review an analysis of the NIDCD's portfolios. This group of extramural scientific experts evaluated the Institute's extramural and intramural portfolios in hearing, balance, smell, taste, voice, speech and language to determine if the mix of scientific disciplines matched the research opportunities in human communication in an advantageous and optimal way. After deliberation and review of the opportunities, they arrived at a consensus that the NIDCD should strengthen its portfolios in the scientific disciplines of molecular biology, molecular genetics, imaging and integrative neuroscience.

These recommendations are already enhancing the NIDCD's research portfolios and will permit us to seize current opportunities such as the one we have now in advancing the biology of brain disorders through research emanating from the discovery of the olfactory map. The sense of smell is mediated by an enormous family of receptor molecules that reside on the surface of the olfactory neurons in the nose. This olfactory receptor multigene family represents more than 1,000 genes. NIDCD scientists are analyzing the molecular determinants of the organization of the olfactory system. They have demonstrated that all neurons expressing a given receptor subtype project their axons, quite amazingly, to just one or two discrete foci within the olfactory bulb. This organization had long eluded investigators approaching the problem through the techniques of other scientific disciplines.

Progress in the molecular genetics of hereditary hearing impairment is accelerating. Only two genes for hereditary hearing impairment were known when the NIDCD was established. Now, over 40 have been found. The work is beginning to shift from finding genes to determining the functional roles of genes in the auditory system. From this work, fundamental new knowledge is evolving on such basic issues as melanocyte migration and differentiation.

Intramural clinical research, using the powerful imaging equipment, available through the Clinical Research Center is demonstrating that cerebral function associated with language may be fundamentally different in persons who stutter. Developmental stuttering, the form of stuttering that persists into adulthood, has been estimated to affect one million Americans. This stuttering interferes with social development, employment and communication. According to scientists in the Neuroimaging Sciences unit, persons who stutter differ markedly in the way in which they formulate and express language. They do not demonstrate the typical left hemisphere dominance seen in control subjects. Instead, brain activity in individuals who stutter is bilateral or predominantly in the right hemisphere. This line of investigation is giving us new information on the mechanisms that control speech and language.

Benign and malignant neoplasms of the upper aerodigestive tract are the most common tumors affecting human communication treated by otolaryngologists-head and neck surgeons. Laryngeal papillomatosis develops in approximately 1,500 children, and head and neck carcinoma develops in more than 75,000 adults each year. Survival rates for these malignant neoplasms has not improved in the last 20 years, and the incidence among women and African Americans has been increasing. The development of these neoplasms and the inhibition of their growth have been the focus of research currently underway. NIDCD scientists have shown that the immune system can be induced to inhibit cancer growth with two cytokines or immune hormones. Additional study is planned to determine whether virally transmitted genes can stimulate production in immune cells and be used for therapy.

Research and development of multichannel cochlear implants, improved speech processors and more effective rehabilitative strategies have all been supported by the NIDCD. NIDCD sponsored a consensus development conference on cochlear implants in adults and children to illuminate the benefits and limitations of cochlear implants. The consensus panel recommended the use of cochlear implants for an additional one million Americans who obtain marginal benefit from hearing aids.

The NIDCD is supporting study of the critical period for language acquisition, focusing on learning American Sign Language and written English by deaf children with different early language-related experiences. Findings from this investigation will lead to better understanding of critical periods for language acquisition and the effect of early bilingualism. These results could have profound impact on educational choices for deaf children.

The Institute is making a five-year commitment to the initiation and conduct of clinical trials through support of cooperative groups. These groups will be comprised of 15 to 20 facilities with clinical research capabilities and experience, poised to answer priority questions. The trials will address efficacy of a wide range of therapy in the mission areas of NIDCD and accelerate our ability to deliver research results to the people as quickly as possible.

NIDCD is engaged in many collaborative efforts with the extramural community, with other NIH institutes and with other Federal agencies. The NIDCD is engaged in an intensive collaboration with the Department of Veterans Affairs (VA) to improve hearing aids. NIDCD, NASA and VA are also collaborating on a search of all Federal laboratories for acoustic and electronic technology that might be applicable to hearing aids. This is an excellent opportunity for the three agencies to work together for important scientific advancement, to ensure non-duplication of effort and with shared financial responsibility.

One of the most rewarding events at NIDCD this year was the first scientific poster session presented by the students, faculty and administrators who are involved in NIDCD's pilot, the Partnership Program developed to maximize opportunities for underrepresented minority individuals to participate in fundamental and applied research in human communication. The NIDCD collaborates with the Office of Research on Minority Health, NIH (ORMH) to support the program. The four centers in the partnership are: the Morehouse School of Medicine/ Atlanta University Complex, the University of Puerto Rico, the University of Alaska System and Gallaudet University. NIDCD will be holding a national meeting in the early fall for all of the participants and will be evaluating the program to provide ORMH with the best possible data about its progress.

When William Shatner appeared before this committee in March, he described the inescapability of tinnitus, a debilitating noise in the ears, a sometimes overwhelming disorder of human communication. For forty-six million Americans, famous or known only to their family and friends, communication disorders are constant distracters in every public and private

moment of the human experience. The NIDCD is grateful for the support it has received and proud of the research it has been able to foster. We are greatly encouraged by the recent results of that research, and I am pleased to have had this opportunity to report to you about the progress made by NIDCD staff and scientists.

The FY 1997 Budget request is \$179,090,000. Thank you for your consideration. I will be happy to answer questions.

REVIEW OF THE RESEARCH PROGRAM

Mr. PORTER. Doctor Snow, as you mentioned, last year you established a Planning and Policy Working Group to evaluate your institute's intramural and extramural research portfolios to see if they matched up well against research opportunities. What were this group's major recommendations? Do they require a shifting of resources among your various research areas? And did the group recommend any adjustment in the relative sizes of your intramural and extramural programs?

Dr. SNOW. The Planning Group has met and has completed their work. They recommended that the portfolios of the NIDCD be strengthened in four areas: in the area of molecular biology, molecular genetics, imaging, and integrative neuroscience. This recommendation was taken to the three principal advisory committees of the institute, the National Advisory Council, the Board of Scientific Counsellors, and the Programs Advisory Committee, and each of these advisory groups endorsed that recommendation. And so, that now serves as guidance to the staff of the Institute as they work on a daily basis with the scientists in the scientific community. It guides the National Advisory Council in its decisions about which grants are recommended to be funded. The advisory group did not recommend any change in the relative proportion between our intramural and our extramural program.

TINNITUS RESEARCH

Mr. PORTER. Doctor Snow, one of our public witnesses this year was the actor William Shatner who expressed his experiences living with tinnitus. He indicated that he thought the disorder was fairly common among workers in the entertainment industry because of their exposure to loud noises. Is exposure to loud noises a risk factor for tinnitus? And should we expect an increase in the incidence of tinnitus as a generation of young people exposed to loud music ages?

Dr. SNOW. Yes, exposure to loud noise is a risk factor for the development of tinnitus. It probably is the most common cause of tinnitus. This is a problem of very great magnitude. There are ten million people in the United States with noise-induced hearing loss. The vast majority of those individuals have tinnitus. There are another twenty million individuals in the United States who are exposed to hazardous noise in the workplace and are at risk of developing noise-induced hearing loss.

Noise-induced hearing loss begins between 10 and 20 years of age, particularly in boys. It is probably not the music that they are exposed to, but rather the intense noise from small arms fire, target practice and hunting being the most important causes. Also, exposure to loud noise in machine shops, woodworking equipment, any internal combustion engine, all of these lead to noise-induced hearing loss when there is exposure to noise without proper ear protection. This is a growing problem, and yes, I believe that there will be more Americans with tinnitus as time goes on. It is very interesting to see the magnitude of the problem. In the latest Interview Study of the National Center for Health Statistics, 18.5 million Americans have tinnitus.

PUBLIC EDUCATION ON EXPOSURE TO LOUD NOISES

Mr. PORTER. Doctor Snow, your institute has developed a public education program for kindergartners through third grade on the dangers of exposure to loud noises. How many schools are using this program?

Dr. SNOW. The "I Love What I Hear" kit has been distributed to approximately 2,500 schools. This program not only teaches about how to protect the ears from exposure to loud noise, but it also introduces the youngsters to the fascinating biology of the auditory system.

Mr. PORTER. And how extensive is the Institute's public education efforts on noise and other hearing-related issues? In other words, what else are you doing in this area?

Dr. SNOW. This is one of our principal activities. We, of course, have opportunity to make public service announcements regarding the damage to the inner ear from loud noise, and customarily do that just before the 4th of July.

Also, when we are interviewed for articles in magazines or newspapers, we always try to make that point.

Mr. PORTER. Mrs. Lowey.

AUTISM RESEARCH

Mrs. LOWEY. Thank you, Mr. Chairman. Thank you, Dr. Snow.

In your testimony you state that you are making a breakthrough in autism. Can you describe this breakthrough in layperson's terms and discuss its relevance to the treatment of autism in children?

Dr. SNOW. The breakthrough that has occurred is that the translocation of a chromosome occurred right where the GRP-R gene is located, and it is possible, that the translocation injured that gene. Perhaps that gene has lost its function.

That raises the possibility that there is a relationship between that gene's function and the problem of autism.

Autism is probably a very genetically complicated problem. There are some indications that other genes are involved in autism, and we think that there are many genes that are yet to be discovered that would play a role.

This is a very early development. We are a long way from recommending either any diagnostic procedures or any treatment.

But, on the other hand, we have had such difficulty finding the genes that relate to language function, we have had such difficulty in getting molecular biology applied to the areas of voice, speech, and language, that we are very much encouraged by this finding and intend to pursue it fully.

Mrs. LOWEY. Thank you. Thank you, Mr. Chairman.

Mr. PORTER. Mr. Miller.

Mr. MILLER. No questions.

Mr. PORTER. Mr. Dickey.

Mr. DICKEY. No questions.

RESEARCH ON SENSE OF SMELL

Mr. PORTER. Dr. Snow, preliminary research into the sense of smell indicates that certain smells may have impacts as varied as speeding learning, improving memory, helping in weight loss, and

bolstering the immune system. Do you think it is possible that research will pinpoint these effects and develop them for clinical use?

Dr. SNOW. Yes. I think there is serious research going on in this area. I don't have anything in particular to share with the committee, but various odors do influence mood, and I think that, with properly conducted research, in time we will know which odorants are effective in producing various moods, and that may have some practical application.

A lot of what you read in the press on the matter is based on hypothesis and not well established by sound scientific studies.

Mr. PORTER. Do we run any risk as a society of being unknowingly manipulated by various smells once these effects are identified?

Dr. SNOW. I think there is that possibility, but I think it's a positive matter. We are manipulated by lighting, and we are manipulated by sound, and it would not surprise me if we are not also influenced in time by odor manipulation.

PARTNERSHIP PROGRAM

Mr. PORTER. Can you tell us more about your partnership with Gallaudet in developing a research training program? We're very supportive of your efforts in integrating Gallaudet into your work and applaud you for doing that.

Dr. SNOW. Thank you. Yes, Gallaudet University is one of the four institutions that we have developed a partnership with. The other institutions are the University of Puerto Rico, the University of Alaska System, and the Morehouse College of Medicine, as a part of the Atlanta Complex.

The idea of this partnership is to bring students, the faculty, and the administrators into the NIDCD for training. Part of the program is to try to improve the curriculum in those institutions in the areas of human communication.

We have had several students from Gallaudet University work in our intramural program, and they have found that to be a rewarding experience. One administrator has come with our extramural program to learn about the granting process and then has returned to Gallaudet University as a member of their staff.

We think this sort of collaboration with Gallaudet University will lead more young people into research careers in human communication, in the auditory area, in particular.

RESEARCH ON SENSE OF SMELL

Mr. PORTER. Your institute supports research into medications similar to anti-allergy drugs that may treat those who have lost their sense of taste or smell. Is this something you foresee being developed in the near term?

Dr. SNOW. Yes. There is work underway at the present time that is studying the use of topical agents, as well as systemic agents, that reduce the swelling of the allergic reaction in the nose to improve the sense of smell. The current status is that the topical application of a corticosteroid is thought to be the most efficacious way of managing that problem. It is also used on a long-term basis to prevent the recurrence of nasal polyposis, one of the three major causes of loss of the sense of smell.

CLINICAL TRIALS

Mr. PORTER. Your testimony, Dr. Snow, mentions the establishment of a network of 15 to 20 clinical trial sites. What will be the major area of focus for this clinical network?

Dr. SNOW. These studies may address any disease that affects hearing, balance, smell, taste, voice, speech, and language. They are the kind of clinical problems that are generally handled by individuals in the professional specialties of otolaryngology, audiology, and speech-language pathology.

COCHLEAR IMPLANT CONSENSUS CONFERENCE

Mr. PORTER. You held a consensus development conference last May on cochlear implants, which you mentioned in your oral testimony. Did the conference suggest any changes in the application for this device?

Dr. SNOW. Yes. A very major change occurred in that consensus development conference in that there was a recognition that many individuals who receive cochlear implants do better at understanding open set speech and lip reading than individuals who receive marginal help from a hearing aid.

If an individual receives less than 30 percent understanding of what is said to them with a hearing aid, they are likely to do better with a cochlear implant, and therefore a rather sweeping recommendation was made that those individuals who receive marginal benefit from a hearing aid—that is, can only understand 30 percent or less—may benefit from a cochlear implant. This is, in the United States, one million individuals.

Mr. PORTER. Mrs. Lowey.

Mrs. LOWEY. No questions.

Mr. PORTER. Mr. Miller, Mr. Dickey.

[No response.]

HEARING AID RESEARCH

Mr. PORTER. How many years away are we from a new generation of hearing aids?

Dr. SNOW. We're making very good progress in hearing aid research. The first clinical trial, in collaboration with the Department of Veterans Affairs, has just begun. It compares the three most commonly-used hearing aid circuits to determine which of the three circuits is most helpful to those subgroups of the hearing-impaired population. This is something that has not been determined, even though some of these circuits have been around for 30 years or more. We are addressing this issue as the first and most important question.

I think the outcome of that clinical trial will make a great difference in the way in which hearing aids are matched to the individuals with a hearing impairment.

We are also supporting a device development contract for new hearing aid technology. We have initiated, in collaboration with NASA, a search of all of the Federal laboratories for acoustic and electronic technology that might be applicable to hearing aids in order to support partnerships among scientists, manufacturers, and Federal laboratories to commercialize those promising technologies.

EARLY IDENTIFICATION OF HEARING IMPAIRMENT

Mr. PORTER. Your institute and others have worked to inform parents of the importance of detecting hearing impairment as early as possible to prevent long-lasting impairments in language development. Over the past five years, has there been any decrease in the average age for detecting hearing impairment in young children?

Dr. SNOW. Not as far as I know. The most recent studies are still those that show that the average age of identifying even profound hearing impairment is two and one half years. It may be time now to repeat that study to see what progress can be measured.

Mr. PORTER. Dr. Snow, you've answered all of my questions very efficiently and the questions of my colleagues. We very much appreciate your testimony here today and the fine job you're doing at the Institute. Thank you for coming to appear.

Dr. SNOW. Thank you very much, sir.

[The following questions were submitted to be answered for the record:]

Research Funding

Mr. Porter: Identify FY 95-97 spending on the following: hearing aid development, otitis media vaccine, Meniere's disease, stuttering, noise-induced hearing loss, tinnitus, spasmodic dysphonia, and dystonia?

Dr. Snow: In hearing aid development, the NIDCD obligated \$2,692,000 in FY 1995; we estimate we will obligate \$2,828,000 in FY 1996; and \$2,911,000 in FY 1997. The NIDCD currently supports over 30 grants related to hearing aid research.

In otitis media vaccine research, in FY 1995 the NIDCD obligated \$5,046,000; we estimate we will obligate \$5,283,000 in FY 1996; and \$5,405,000 in FY 1997. Nontypeable *Haemophilus influenzae* (NTHi) is a major pathogen causing otitis media in children. The development of a vaccine against otitis media, particularly that caused by NTHi, would provide an immune response in infants and young children who could be protected against otitis media which is the major cause of acquired hearing impairment in childhood. A vaccine would reduce the otitis media morbidity and health care costs significantly. The societal costs of otitis media account for over 10 million visits to physicians each year for both the child and parents, with associated health care costs estimated in the billions of dollars. These studies will further our development of an effective vaccine or intervention strategy against otitis media.

In Meniere's disease, the NIDCD obligated \$882,000 in FY 1995; we estimate we will obligate \$918,000 in FY 1996; and \$939,000 in FY 1997. Meniere's disease is an abnormality of the inner ear causing a host of symptoms, including vertigo or severe dizziness, tinnitus or a roaring sound in the ears, fluctuating hearing loss, and the sensation of pressure or pain in the affected ear. The disorder is a common cause of hearing loss.

In stuttering research, the NIDCD obligated \$1,227,000 in FY 1995; we estimate we will obligate \$1,296,000 in FY 1996; and \$1,327,000 in FY 1997. NIDCD intramural scientists have determined that in a family with cluttered speech that females were affected less often than males, but affected females had different expressions from those of the males and they exhibited spontaneous recovery. Further research is planned in not only the area of cluttering but also possible learning deficits in individuals who stutter.

In noise-induced hearing loss, the NIDCD obligated \$4,532,000 in FY 1995; we estimate we will obligate \$4,734,000 in FY 1996; and \$4,851,000 in FY 1997. NIDCD will continue research that investigates age-related cochlear microcirculatory changes; studies molecular biologic changes in age-related hearing loss; and attempts to attenuate presbycusis via free oxygen radical scavenging and blocking agents. The health relatedness of this project is apparent considering that more than 30 million Americans suffer from significant sensorineural hearing loss. As our population ages, this number will increase rapidly.

In tinnitus research, the NIDCD obligated \$90,373,000 in FY 1995; we estimate we will obligate \$95,279,000; and \$97,517,000 in FY 1997. Tinnitus is a

condition that affects 15-20 million Americans, including a significant number whose tinnitus precludes normal occupational and social activities. Research on virtually any aspect of the healthy or disordered auditory system may be applicable to some form of tinnitus.

In spasmodic dysphonia research, the NIDCD obligated \$582,000 in FY 1995; we estimate we will obligate \$618,000 in FY 1996; and \$634,000 in FY 1997. The NIDCD Intramural Research Program is developing a clinical protocol to define more accurate diagnostic criteria for spasmodic dysphonia resulting from neuronal rather than psychological causes. Investigators plan to begin a search for genes which may predispose persons to develop spasmodic dysphonia. The only form of dystonia for which the NIDCD supports research is spasmodic dysphonia.

Public Information Activities

Mr. Porter: How much does your 1997 budget include for public information activities?

Dr. Snow: The NIDCD will obligate an estimated \$775,000 in FY 1997 for public information activities. Included in the activities are the NIDCD congressionally mandated Information Clearinghouse and a wide array of activities directed toward professional, medical, public and patient organizations for the effective dissemination of important research results and disease prevention and health promotion messages.

Clinical Trials

Mr. Stokes: Overall, how much is included in FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Snow: In clinical trials, the NIDCD obligated \$6,177,000 in FY 1994 and \$9,427,000 in FY 1995. We estimate we will obligate \$10,241,000 in FY 1996; and \$10,495,000 in FY 1997.

Mr. Stokes: What is the Institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Snow: NIH policy requires that women and minorities be included in all human subject research, and the NIH Revitalization Act of 1993 requires monitoring of inclusion. In response to the Revitalization Act and to the 1990 GAO Report, a centralized database was developed by the DRG to assist in tracking demographic data on gender/minority inclusion. In January of 1995, each Institute was asked by the Office of the Director, NIH, to provide this information for all supported Phase III clinical trials. An NIH-wide committee, Tracking of Women and Minorities in Clinical Research, sponsored by the Office of Research on Women's Health, was established to coordinate this response. Each month, the committee meets to discuss further implementation of the gender/minority tracking system. NIDCD is represented in each of these meetings.

Mr. Stokes: Last year, the Institute reported to the committee concerning four major clinical trials: cochlear implant and tactile aid studies in deaf children; identification of neonatal hearing impairment; neurogenic communication disorders; and treatment of sentence-processing disorders in aphasia. What progress do you have to report this year on the status of each of these trials?

Dr. Snow: In the cochlear implant and tactile aid studies in children, results continue to demonstrate the importance of studying speech production changes in cochlear implant users for many years, as the overall speech intelligibility of the cochlear implant subjects continues to improve after more than 3.5 years of multichannel use. The results also continue to have important implications for candidacy criteria for cochlear implants in children and for selection of an appropriate educational environment.

In the identification of neonatal hearing impairment study, the goal was to develop optimal procedure for neonatal hearing screening. The project has now enrolled approximately 75% of the 7200 babies to be included in this multisite study. Behavioral follow-up studies are underway.

In the treatment of sentence processing disorders in aphasia, the goal was to develop and ascertain the efficacy of treatment protocols for the disorders of sentence processing and production in individuals with aphasia. Eleven single subject experiments have been completed and five more are in progress. Preliminary results indicate improvements in language with the experimental treatment.

The neurogenic communication disorders study, a subproject of a large scale multipurpose research and training center, focuses on the effectiveness of selected rehabilitation techniques for reducing perseveration in aphasic stroke patients, patients with Parkinson's disease, and Alzheimer's disease patients. Patient recruitment and treatment continues; 30 have entered the treatment phase of the study.

Aging Research

Mr. Stokes: Briefly, what major research activities are underway with respect to seniors? How much is included in the budget for this research initiative and how does it compare to FY 1996 and FY 1995?

Dr. Snow: In addition to its continuous research on those conditions that generally affect older Americans, such as presbycusis, tinnitus, as well as research on the improvement of hearing aid technology and assistive devices, NIDCD-supported investigators are exploring the pathophysiologic factors potentially related to hearing capabilities in older women, in an effort to better understand gender-specific presbycusis. One factor includes the relation between incidence of hearing loss and cardiovascular risk factors. Approximately \$8,334,000 will be available in FY 1997 for aging research; in FY 1996, an estimated \$8,115,000 will be available and \$7,739,000 was obligated in FY 1995.

Minority Research

Mr. Stokes: For the diseases and disorders that are under the purview of your Institute, where do we stand today with respect to closing the gap in minority health, specifically what progress do you have to report to the subcommittee this year? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Snow: Numerous initiatives are in place or being planned, which address minority health issues, as exemplified by the following items. The NIDCD, in collaboration with the Office for Research on Minority Health, is planning a workshop on Aphasia and Stroke in Minority Populations. Two research grants are exploring the language and language disorders of African-American children. Another NIDCD grant is examining a number of issues related to hearing in Americans of Cuban, Mexican and Puerto Rican descent, information that will be crucial in the development and implementation of intervention programs in the Hispanic population. An ongoing initiative continues to bring in applications on identification and treatment of language impairments in multicultural populations.

The active participation of NIDCD in the Minority Supplement program is providing minority investigators an opportunity to address issues related to minority health, as a spin-off or supplement to the main theme of the parent grant.

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your Institute?

Dr. Snow: The NIDCD has a number of initiatives in place or being planned for implementation in this fiscal year, which promise to increase the number of minority researchers in human communication. One soon to be issued Request for Applications, offered in conjunction with the Office for Research on Minority Health, is "Minority Dissertation Research Grants in Human Communication", which offers Small Grants to support doctoral dissertation research in human communication for minority doctoral students. Up to 10 grants, for two years of support, will be awarded. Another initiative, "Mentored Research Scientist Development Award for Minority School Faculty" will support the research career development of faculty members at minority academic institutions over a period of three, four or five years, to foster research in human communication. The program of Research Supplements for Underrepresented Minorities continues to be quite active in NIDCD and a number of new undergraduate and graduate students as well as minority investigators are being supported this fiscal year. The Travel Fellowships for Underrepresented Minority Students in Communication Sciences and Disorders remains active and this past year saw many students participating in important scientific meetings because of support received through this program. It is expected that such participation will encourage continued involvement by minorities in research.

Mr. Stokes: What collaborative efforts are underway with your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the Office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Snow: The NIDCD and the Office of Research on Minority Health (ORMH) collaborate on several projects: 1) In FY 1996 the ORMH will provide \$300,000 to NIDCD to issue a Request for Applications (RFA) for the purpose of providing approximately 10 grants to support doctoral dissertation research for minority doctoral candidates. 2) Community Child Health Research Network will develop and conduct studies to decrease infant mortality and morbidity and improve child health in American Indian/Native Alaskan and other urban and rural communities through a network of community based clinical study centers and a central data coordinating and analysis center. In FY 1996, \$75,000 will be provided by ORMH to support this collaboration. 3) The Mentored Research Scientists Development Award (K01) for Minority School Faculty will foster the career development of faculty investigators at minority institutions in human communication research and to encourage the entry of investigators from minority groups into human communication research. In FY 1996, \$459,000 will be provided

by ORMH to support this initiative. 4) The Partnership Program is a comprehensive minority research and training demonstration program between the NIDCD and four academic institutions. The partnership is maximizing opportunities for underrepresented minority individuals to participate in fundamental and clinical research on hearing, balance, smell, taste, voice, speech, and language. In FY 1996, \$450,000 will be provided by ORMH to support this project. 5) The Howard University Center for the Study of Aphasia and Stroke among African Americans. This proposed center would promote research on communication disorders (aphasia) resulting from cerebrovascular accidents (strokes) among African Americans. In FY 1996, \$200,000 will be provided for this program by ORMH. The NIDCD contributions to these collaborations are staff time, equipment, and supplies.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the Office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the Office.

Dr. Snow: Currently, the NIDCD does not co-fund any projects with the ORMH.

Hearing Aid Research

Mr. Stokes: Last year, NIDCD sponsored the first biennial hearing aid research and development conference, the first national meeting of its kind, what was the purpose of the meeting and how does it fit into your overall collaborative efforts with the department of veterans affairs?

Dr. Snow: In September 1995, the NIDCD and the Department of Veterans Affairs cosponsored the First Biennial Conference on Advancing Human Communication: An Interdisciplinary Forum on Hearing Aid Research and Development. The objectives of the conference were to share and critically examine current research relevant to speech understanding with amplification and signal processing in noise and quiet. The conference was intended to encourage research to pursue the questions, issues and priorities identified at this meeting. These endeavors are critical to future progress in hearing aid research and development. Therefore, it is expected that the outcome of the conference can only strengthen the collaborative efforts of the two agencies.

Hereditary Hearing Impairment

Mr. Stokes: With respect to molecular genetics, the Institute has made important strides in the area of hereditary hearing impairment. What progress do you have to report to the committee this year?

Dr. Snow: The NIDCD has made great progress in the area of molecular genetics of hereditary hearing impairment. In 1989, the year NIDCD was established, only two genes for hereditary hearing impairment were known. Since then over 40 have been found. Not only has the research focus been on finding genes, but also on determining the functional roles of genes in the auditory system. As a result, fundamental new knowledge is evolving in such basic issues as melanocyte migration and differentiation.

Partnership Program

Mr. Stokes: Last year, you told us about a new partnership program with minority institutions, what can you tell us this year about the program?

Dr. Snow: The NIDCD Partnership Program was established as a comprehensive minority research and training demonstration program between the NIDCD and four academic institutions: the Morehouse School of Medicine/Atlanta University Complex, the University of Alaska System, the University of Puerto Rico, and Gallaudet University. These institutions have large enrollments of minorities currently underrepresented in the area of biomedical and behavioral research. Students who are deaf or hard of hearing are included in this program as they are also currently underrepresented in these areas of research. Through a Memorandum of Understanding (MOU) between the NIDCD and the NIH Office of Research on Minority Health, the program has provided support for improvement of curriculum and current research activities and for the exchange of students, scientists, and administrators at the four institutions.

The program is in its third year, and student research results have already been presented at two NIDCD Research Festivals and the University of Puerto Rico Medical School and the University of Alaska.

Public Education Activities

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at you Institute? How much is included the FY 97 budget for the Institute's outreach and public education programs, and how does it compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Snow: Planned NIDCD public information activities for FY 1997 include materials that alert parents, grandparents and other caregivers and health professionals to early signs of hearing, speech and language impairment in infants and young children. Specific campaigns are going out to state health agencies and to Native American tribal leaders as well as to resource centers that will reach urban native Americans. Specific elements of the campaign are directed to African-American and Pacific-Asian-American and Hispanic/Latino-American populations, often missed by other identification efforts. These efforts are in concert with community health groups and organizations. Additionally, the NIDCD will collaborate with the National Association for the Deaf and other deafness-related

organizations in developing leader materials for prevention of AIDS in the deaf community. This audience poses special problems related to low literacy and poor communication on the topic.

NIDCD will continue its efforts in the prevention of noise-induced hearing loss, using a videotape and teacher curriculum guide called "I Love What I Hear!" directing the message to school children between the ages of 8 and 12. Another effort is in development for FY 97 to reach Hispanic/Latino-American teenagers with a message about prevention of noise-induced hearing loss.

Working with the 130+ organizations listed in NIDCD's directory of organizations with missions related to hearing, balance, smell, taste, voice, speech or language issues or diseases, using a "tiered" approach to cost-efficient dissemination to the public and focusing on regional opportunities, the NIDCD will increase its contact with patients, health professionals and the public.

An example of this effort is the cooperation with health volunteer and professional organizations so that appropriate materials can be duplicated and distributed effectively to their members.

NIDCD information will be made available through home page access in May 1996 and will make information accessible in the areas of normal and disordered processes of hearing, balance, smell, taste, voice, speech and language including the most recent research results.

The NIDCD will obligate an estimated \$318,000 on outreach and public information activities in FY 1997; as compared to \$318,000 in FY 1996; \$382,000 in FY 1995; \$235,000 in FY 1994.

Mr. Stokes: In most of the Institutes, as these programs are funded in research management and support account, is this the case in your Institute? If yes, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are you hurting the most?

Dr. Snow: In the NIDCD, outreach activities are funded through the research management and support line, and public information is funded through the research management and support line and through the research and development contract line for the NIDCD Information Clearinghouse. We have developed the materials necessary for major public education efforts to ensure early identification of children with hearing, speech and language disorders and prevent hearing loss in teenagers and young children but will be severely limited in our ability to disseminate the materials and reach all necessary audiences.

JUSTIFICATION OF THE BUDGET ESTIMATES

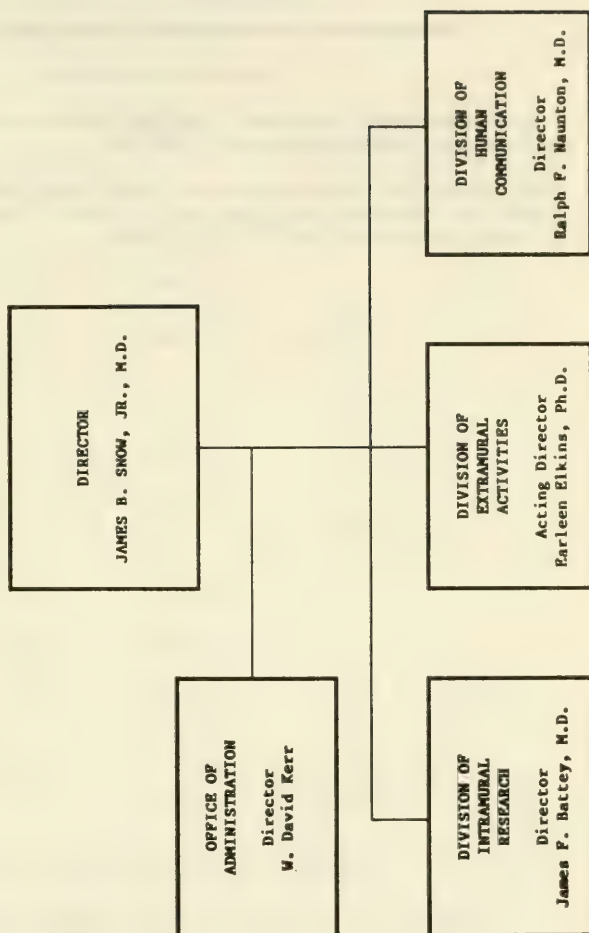
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

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NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS



NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

For carrying out Section 301 and title IV of the Public Health Service Act with respect to deafness and other communication disorders, \$179,090,000.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Amounts Available for Obligation ^{1/}

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$166,886,000	\$176,502,000	\$179,090,000
Reduction in accordance with P.L. 103-333.....	(125,000)		
Rescission in accordance with P.L. 104-19.....	(101,000)		
Subtotal, Adjusted Appropriation.....	166,660,000	176,502,000	179,090,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	(142,000)		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....		(1,650,000)	
Comparative transfer from: OD NIH for two FTEs.....	215,000		
Other NIH Institutes for Management Fund adjustment	405,000		
Subtotal, adjusted budget authority.....	167,138,000	174,852,000	179,090,000
Unobligated balance, lapsing.....	(56,000)		
Total obligations.....	167,082,000	174,852,000	179,090,000

1/ Excludes the following amounts for reimbursable activities carried out by this account
FY 1995 - - \$2,766,000; FY 1996 - - \$4,300,000; FY 1997 - - \$4,300,000.

Also excludes funding for HIV activities: FY 1995 - - \$1,552,000; FY 1997 - - \$1,726,000,
included in the Office of AIDS Research, NIH.

Note: Excludes \$34,887 in FY 1995 and \$32,000 in FY 1996 for royalties.

National Institute on Deafness and Other Communication Disorders

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
125	\$167,138,000	134	\$174,852,000	134	\$179,090,000	---	\$4,238,000

Introduction

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute on Deafness and Other Communication Disorders. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute on Deafness and Other Communication Disorders (NIDCD) is responsible for conducting and supporting research in human communication. Included in the program areas are research and research training on normal and disordered mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. The NIDCD is actively involved in health promotion and disease prevention.

The NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute also supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

Extramural Research

Cochlear Implant Technology

The development of the cochlear implant, a prosthetic device that changes sound into electrical impulses in order to stimulate auditory nerve fibers, has given individuals with profound hearing impairment new or renewed communication abilities.

The NIDCD has been a major supporter of research and development of multichannel cochlear implants. The implant has been an important step in NIDCD's long-range goals of understanding, preventing, and treating hearing impairment and resulting language disorders. The Institute also conducts and supports research on diseases and conditions associated with hearing loss and develops and implements health promotion programs to disseminate research results.

More than 12,000 children and adults in the United States have received a cochlear implant. The current cost of an implant, projected over a lifetime, is about \$500 per year. The implant has a 3:1 cost advantage over other rehabilitative strategies. Expanded occupational choices could raise the cost advantage to 6:1.

Users of the implant consistently describe highly improved communication ability and quality of life. With cochlear implants, postlingually deaf adults experience improved speech reading and many are able to recognize words without visual cues. Post-implant improvements in speech perception and production have been reported. In a recent study, psychological evaluations were conducted on 30 postlingually deafened adults pre- and post-implantation. After 18 months of implant use, the recipients showed a significant reduction in depression, loneliness, social anxiety, suspiciousness, and social isolation.

NIDCD continues its commitment to support efforts to create and improve devices that substitute for lost and impaired sensory and communication functions. This is evidenced by its broad support of research that includes the development of hearing aid devices; longitudinal evaluation of communication skills of children with single- or multi-channel cochlear implants; development of a new type of speech processor for cochlear implants; and optimization of the design, effectiveness, and potential side effects of an auditory brainstem implant, which is an electronic prosthesis similar to a cochlear implant positioned in the brainstem.

The NIDCD, together with the Office of Medical Application of Research, convened a NIH Consensus Development Conference on Cochlear Implants in Adults and Children on May 15-17, 1995. Co-sponsored by the National Institute on Aging, the National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, and the Department of Veterans Affairs, the conference summarized current knowledge about the range of benefits and limitations of cochlear implantation. One of the major conclusions of the panel addressed the auditory criteria for adult implant candidacy. Previously, only adults with profound hearing impairment were candidates for implantation, and individuals receiving marginal benefit from hearing aids were not considered implant candidates. However, recent data show that most marginally successful hearing aid users will have improved speech perception performance with a cochlear implant. The panel therefore concluded that it is reasonable to extend cochlear implants to postlingually hearing-impaired adults currently obtaining marginal benefit from other amplification systems, increasing the number of Americans to some one million who may benefit from a cochlear implant.

Literacy in Deaf Individuals

Current studies are focused on the acquisition of American Sign Language (ASL) and written English by deaf children with different early language-related experiences. Some of these children have deaf, signing parents. Typically, they learn ASL in a manner similar to that followed by hearing children in acquiring their native languages; often their skills in written English are superior to other deaf children. Some of the children under investigation do not begin to receive input in ASL until school age; their acquisition of ASL is delayed and quite often incomplete. A third group being studied comprises children who begin to receive input in ASL relatively early, though not at birth, from their hearing parents. Preliminary results from native and early signers show only small differences in both languages. When data collection in these studies is completed, it will be possible to compare age at first exposure to ASL with degree of acquisition of ASL or English. These research findings will contribute to our

understanding of the nature of the critical period for language acquisition and the effectiveness of early bilingualism and will have a profound impact on the educational choices for deaf children, since early intensive ASL intervention is currently rare.

Putting Research into Practice through the SBIR and STTR Programs

The Small Business Innovation Research (SBIR) program was authorized by Congress in 1982, and currently 11 Federal agencies, including the Department of Health and Human Services, are program participants.

Representative products brought to commercialization by NIDCD awards through this program include: vibrotactile devices for the deaf, a multiple modality assistive listening device, an automated evoked potential audiometry system, a balance assessment system, a computerized fluency trainer and sign language software. Some examples of projects that are ongoing or have not reached the commercialization stage yet include: development of a low-cost, portable telecommunications device (TDD) for the deaf; development of a high-performance headset hearing aid; development of a microphone processor system to improve the signal-to-noise ratio and the directionality of tactile communication aids, hearing aids and cochlear implants; a robotic fingerspelling device for individuals who are deaf and blind, to allow face-to-face communication with those who do not know how to fingerspell; the development of speech synthesis software for five dialects of American English for use in a range of vocal communication aids from aids for severely vocally-impaired individuals to those used in office information systems; improved augmentative and alternative communication devices for individuals with speech problems to be able to communicate effectively and interactively in a variety of environments with diverse partners; and a computer-based speech training system designed to assist individuals in learning to speak English as a second language.

Established as a three-year pilot program in FY 1994, the Small Business Technology Transfer (STTR) Program encourages cooperative research and development between small businesses and research institutions. NIDCD awarded an STTR grant in FY 1994 to develop high-density electrode arrays for use in cochlear implants. In FY 1995, a grant for the design of an augmentative communication aid using natural language processing techniques to facilitate the generation of longer, syntactically correct sentences for those with cognitive impairments and expressive language difficulties, and another for the development of a three-dimensional system for use in teaching American Sign Language to individuals with hearing impairments and others working in the field of deafness were awarded.

Looking for Answers to the Symptom of Tinnitus

Tinnitus, the subjective perception of sound in the absence of an objective stimulus, is a condition that affects at least ten million people in the United States. Although it is a significant national health problem, affecting millions of people to the point that normal occupational and social activities are interrupted or precluded, there is a lack of research addressing specific causes of this symptom that is related to many different forms of hearing impairment.

A workshop on "Defining Future Directions for Tinnitus Research" was held in March 1995 and provided an opportunity for scientists and clinicians, whose research or patient care responsibilities directly relate to auditory system function, to provide input to the NIDCD on future research directions in this area. There was agreement on a variety of research areas that could shed light on mechanisms producing tinnitus, and the institute plans to publish an initiative incorporating many of the workshop's recommendations.

Native American Children and Their Risk of Otitis Media

While retrospective studies of middle ear status suggest that Native Americans have a higher prevalence of otitis media (OM) than the general U.S. population, there is only one prospective study of OM incidence rates and associated risk factors in Native American children. While some information is available from this study on acute OM, data on chronic forms of this disease and associated risk factors are lacking. While many risk factors for OM have been identified in the general population, the applicability of these studies to Native Americans is unknown. Understanding both the natural history and relative importance of risk factors is vital in gaining insight into OM epidemiology in both majority and minority populations.

An NIDCD-funded study is examining risk factors for OM in Native American mothers and their children at the White Earth Reservation in Minnesota. A series of questions will be posed to the mothers which will examine their knowledge and attitudes about OM, health beliefs and practices, and the prevalence of previously established OM risk factors.

Discovering the Gene for Usher Syndrome Type Ib

Usher Syndrome is a devastating disease which affects both sight and hearing. As such it is a major cause of combined deafness and blindness in the United States. There are three identified clinical subtypes of Usher syndrome, with the major differences being in the age of onset and severity of the hearing impairment, and the presence of vestibular deficits (which only occur in Usher type I). There are at least 3 different genes in which defects can result in Usher syndrome type I. One of these genes, on chromosome 11q (Usher type 1b), is responsible for over 70 percent of all Usher type I cases, and is therefore a major contributor to the incidence of combined deafness and blindness.

Hearing Loss and Its Effect on Older Women

Projections based on figures from the National Center for Health Statistics estimate that by the year 2030, at least 21 million Americans beyond 65 years of age will be classified as hearing impaired. Age-related hearing loss (presbycusis) is a seemingly complex disorder developed in senior years, typically characterized by a decrease in speech understanding, though not necessarily a parallel decrease in sensitivity to simple tones. The functional consequences of hearing loss in senior citizens, as evidenced by its impact upon psychosocial well-being, can be substantial. This is particularly true for elderly women since during their latter years an increased susceptibility to a variety of conditions of aging seems only to further the functional impact of

the hearing loss. To gain a better understanding of gender-specific presbycusis, NIDCD-supported investigators are exploring the pathophysiologic factors potentially related to hearing capabilities in older women. Such factors include, for example, the relation between incidence of hearing loss and cardiovascular risk factors.

Improving Our Hearing Aid Technology

While over 25 million Americans suffer some degree of hearing impairment, only about 20 percent of that number have hearing aids. The NIDCD currently supports over 40 grants related to hearing aid research and development. This work ranges from the application of new signal processing strategies to improve sound transmission with less interference from noise to psychophysical studies of the impact of abnormal frequency selectivity on speech recognition in normal and hearing-impaired listeners.

The NIDCD and the Department of Veterans Affairs (VA) are continuing an innovative collaboration designed to support the development of better hearing devices. A contract for a program of device development for hearing aids to support the design and evaluation of creative new technologies and strategies for hearing aids was awarded in July 1995. A clinical trial is expected to begin in 1995. The trial will allow for the determination of subgroups of hearing impaired individuals who benefit most from existing and newly developed hearing aid technologies. The first of the biennial hearing aid research and development conferences was held in September 1995. This national forum for the presentation of research relevant to hearing aids was very well attended and promises to become a meeting of national and international importance to those in fields related to hearing aid research and development.

Central Auditory System Plasticity in Adults

In contrast to traditional beliefs, the auditory cortex is now known to be physiologically dynamic, or plastic, in the adult. The response properties of its neurons are governed not only by the physical parameters of acoustic stimuli but also by their acquired behavioral significance. This ability to change is highly specific, develops very rapidly, occurs for different learning paradigms, and can last indefinitely.

While it is accepted that the central nervous system remains plastic throughout the lifespan, the mechanisms underlying this plasticity are unclear. The time course for these changes is variable, and may be due to the growth of axons and the formation of new connections over long distances or due to alterations in synaptic strength and the "unmasking" or activation of subthreshold pathways. Two laboratories supported by the NIDCD are poised to begin the study of mechanisms subserving plasticity in the adult auditory system.

The roles of drug and nondrug therapies for the recovery of function following peripheral or central injury or disease and their relationships to plastic changes in the central nervous system are being explored. For example, the ability of nerve growth factors to enhance functional brain recovery following stroke is being studied in humans. The role of physical therapy in the recovery of motor function and observed changes in motor cortical regions is also being

examined. Such studies of adult central auditory system plasticity promise to lead to a better understanding of normal brain function and development as well as to explain the recovery of auditory function sometimes seen following injury to the auditory system. In addition, these studies have the potential to reveal how auditory learning occurs, including that often seen following cochlear implantation. Findings may also direct the development of therapies for recovery of function following brain injuries, diseases, and disorders that affect auditory perception.

Hair Cell Regeneration in the Auditory and Vestibular Sense Organs

Loss of the hair cells of the inner ear can occur as a result of noise exposure, treatment with certain drugs toxic to the inner ear sensory cells (e.g. aminoglycoside antibiotics), or with aging, and is the leading cause of hearing loss and balance disorders. It has been known for several years that the auditory and vestibular hair cells of nonmammalian vertebrates, such as amphibians and birds, regenerate following drug and/or noise-induced injury. Recently it has been demonstrated that a similar process of regenerative proliferation occurs in organ cultures of the adult mammalian (guinea pig and human) vestibular sense organs as well, suggesting that hair cell regeneration is a general feature of the vertebrate ear. Much research effort supported by the NIDCD is being directed to identify the specific factors that trigger and regulate the regenerative process and to determine whether the regenerated hair cells are functional. Specific growth factors that play a role in the proliferation of vestibular supporting cells have recently been suggested. A remarkable degree and specificity of structural recovery has been demonstrated over a period of months for auditory and vestibular hair cells in the bird. The original types and near normal numbers and sizes of hair cells have been restored, with only slight abnormalities in the hair cell mosaic. Moreover, eight weeks after aminoglycoside toxicity, the regenerated vestibular hair cells in the bird restore essentially normal function to the horizontal vestibulo-ocular reflex. This recovery of function was highly correlated with the return of hair cells to the vestibular sense organ driving this reflex, the horizontal semicircular canal. This dramatic finding raises the possibility that functional recovery of the vestibular sense organ damaged by trauma or disease may occur in higher mammals.

NIDCD-NASA Center for Vestibular Research

In August 1993, the NIDCD and the National Aeronautics and Space Administration (NASA) jointly awarded \$1 million per annum for five years of support for a ground-based, multi-institutional center to carry out an integrated research and research training program centered around the vestibular control of balance during standing, locomotion and other purposeful movements. Two of the Center's research projects focus on the roles of the inner ear vestibular receptors in the control of balance, and three research projects focus on the vestibulocollic reflex, an important vestibular-driven mechanism for controlling stabilization of the head relative to the trunk during motion.

Integral to the Center's research enterprise is the development of computational models of the sensory-to-motor transformations relating the vestibular driven balance control system to its neural substrates. A detailed, anatomically based biomechanical model of the human head and

neck musculoskeletal system, currently including 20 pairs of neck muscles that control about 8 joints, has been developed and will soon be accessible to the scientific community on the Internet World Wide Web. This model is constructed from parameters obtained through computer representations of human-neck biomechanics and from the muscle properties observed in cadaver specimens.

Multiple Functional Roles for the Olfactory Multigene Family

An enormous amount of genetic information is devoted to the olfactory multigene family and scientists have now begun to ascribe new functions to these receptor molecules in addition to their role in detecting odors in the nose. Recent studies suggest that olfactory receptors are expressed in locations outside the nose where they serve a broad role in sensing the chemical environment. For example, findings indicate that mature sperm express olfactory receptor molecules, suggesting that the receptors may be involved in sensing the chemical environment and thus enable the sperm to correctly identify and move toward the egg.

The sense of smell is currently believed to be mediated by an enormous family of receptor molecules that reside on the surface of sensory neurons deep in the nose. The olfactory receptor multigene family is the largest gene family thus far identified in mammals. NIDCD-supported scientist have recently identified several additional roles for olfactory receptor molecules. These molecules may be involved in chemical sensing of the environment, a broad function that extends beyond the specific role of odor detection in the nose. Subsets of olfactory sensory neurons can be classified by the receptor molecule they contain. By analysis of these protein sequences, it has been demonstrated that the receptor molecule could serve a dual role, sensing odor molecules in the nose and guiding the axon toward its target in the brain. A portion of the receptor molecule has been shown to contain a unique identifier sequence that may carry information about the receptor's sensitivity to different odors and thus provide the basis for a functional odor map in the brain.

Taste Changes in Women With Gestational Diabetes Mellitus

Gestational diabetes mellitus is the most common complication of pregnancy. It affects 1-5 percent of all pregnant women, although prevalence rates in minority populations can exceed 12 percent. NIDCD is supporting research in women recently diagnosed with gestational diabetes mellitus to examine taste responses and diet during pregnancy and after delivery in order to document taste changes that are distinct from those of normal pregnancy and to determine whether these changes persist after delivery. The aim of these studies is to develop new dietary intervention strategies for pregnant women with this disease.

Genetic Studies of Language Impairment

Numerous studies have recognized familial aggregation of language deficits in primary family members of children with language impairments. However, the vast majority of these data derive exclusively from self-report questionnaires. Few direct evaluations of the parents and siblings of

language-impaired children have been obtained, thus limiting our understanding of types and severity of disorders in family members.

Investigators are examining the genetic basis of specific developmental language impairment. Case-control research designs are being used as investigators seek to determine whether there is significant family aggregation of processes associated with developmental language impairment among the primary relatives of language-impaired children and, if there is, whether the rates and patterns of expression are compatible with any known modes of genetic transmission. In addition, efforts are continuing to determine whether temporal processing disorders meet the criteria of a "biological trait marker" that could be used for classifying family members of language-impaired probands as affected or unaffected. This differentiation will be important in future molecular genetic research.

Effects of Signing on Speech During Simultaneous Communication

Deaf communities in the United States have two primary modes of signed communication: American Sign Language (ASL), which is a natural language used by some individuals who are deaf, and various forms of signed English, which are artificial systems created by the hearing communities primarily for teaching purposes and which are used by deaf individuals for the purpose of communicating with hearing individuals. The simultaneous production of spoken English and Signed English, termed "simultaneous communication" (SC), was designed in the hope that constant contact with speech would decrease the need for speech training for deaf individuals and that experience with signs would assist them in the comprehension of English. However, researchers and educators have expressed concern about disruptions of speech and signing during SC. NIDCD investigators have been studying bimodal communication (speech and signing) in deaf individuals to determine how simultaneous signing affects speech. Preliminary results suggest that when trying to sign and speak, normal hearing individuals exhibit differences from speech alone, for example, in the number of gaps between words, duration of syllables, and duration of gaps, as well as in speech amplitude. The observed distortion, occurring in speech during simultaneous communication with signed English, strengthens the concerns being raised regarding the efficacy and viability of simultaneous communication as an effective tool for teaching language and educating deaf children.

Development of Language and Language Disorders in Speakers of Black English

The United States is a multicultural society with many diverse languages and dialects. Historically, many children who are not speakers of Standard English have been misdiagnosed as learning disabled, communicatively handicapped, or cognitively deficient when in fact they are only culturally and linguistically different. There are inadequate assessment and treatment methods for this population which would allow accurate identification and management of language disorders and language differences. In particular, although syntactic and phonologic patterns characteristic of Black English have been documented, identification of language disorder in speakers of Black English remains problematic. NIDCD researchers are developing a criterion-referenced assessment for identifying and describing language disorders in this population. In addition, these researchers are extending current knowledge about the

characteristic features and constraints governing Black English. These investigations will have a major impact on the identification and provision of remedial treatment to children with language impairment.

Intramural Research

Cytokines and the Pathogenesis and Progression of Vocal Tract Squamous Cell Carcinomas

Benign and malignant neoplasms of the upper aerodigestive tract are the most common tumors affecting human communication. Laryngeal papillomatosis develops in approximately 1,500 children and young adults, and head and neck carcinoma develops in about 75,000 aging adults annually in the U.S. Adequate therapy often results in scarring or removal of portions of the organs involved in voice and speech production, with a loss of function that often cannot be entirely reconstructed. Worse still, there has been no improvement in the death rate from these neoplasms (20,000 annually) in the past 20 years, and rates among women and African Americans have been increasing. Scientists from the Head and Neck Surgery Branch, NIDCD, are studying the development of these neoplasms in order to devise new approaches to prevention, diagnosis and therapy.

Investigators in the Tumor Biology Section of the Head and Neck Surgery Branch, NIDCD, have shown that two cytokines (immune hormones) can induce the immune system to inhibit growth of these tumors. Cytokines interleukin 2 and interleukin 12, which can induce killer T lymphocytes, appear to hold the most promise for immunotherapy for these tumors. A third cytokine, interferon gamma, has a direct inhibitory effect upon growth of the tumor cells. These cytokines have an even greater effect on growth and prolongation of survival in a second experimental model of the neoplasm tested during the past year. Investigators have designed and developed a nonreproducing virus to package and transfer the genes that encode the cytokines to the tumor cells. This strategy provides the needed signals to target tumor cells for destruction by the immune system. Additional studies are needed to determine whether the virally transferred cytokines can stimulate immune cells obtained from patients and be useful for human therapy.

Development of a Candidate Vaccine Against Otitis Media

Otitis media is a major public health problem facing children and the associated annual cost for medical care in the United States alone is estimated to be in the billions of dollars. Nontypeable *Haemophilus influenzae* (NTHi) is a major pathogen causing otitis media in children. A dramatic increase in the incidence of multi-drug resistant strains of bacteria that cause otitis media underscores the urgency of developing a vaccine against these microorganisms. The Otitis Media Vaccine Unit in the Laboratory of Cellular Biology, NIDCD, has successfully prepared a detoxified lipooligosaccharide (dLOS)-based conjugate antigen from NTHi. This conjugate antigen induces a bactericidal humoral immune response in two animal model systems making it a potential vaccine candidate. Plans are underway to initiate a phase I clinical trial of this promising vaccine candidate.

Identification of Genes That Can Cause Inherited Hearing Impairment

Approximately one child in 1000 is born with hearing impairment, much of which has a genetic basis. While notable progress continues to be made in identifying the genes involved in hereditary hearing impairment, many of these important genes have not been mapped to date. Two novel loci for nonsyndromic hereditary hearing impairment have been mapped by investigators in the Laboratory of Molecular Genetics, NIDCD, using gene linkage analysis methodology. One locus is found on chromosome 4p in the region of the Huntington's disease gene. This locus causes a dominant progressive low-frequency hearing loss in a large extended family in the United States. The region of linkage spans a distance of approximately 500,000 base pairs, which could be reduced when additional polymorphic markers are examined. There is a possibility that mutations in known sequences, mapped during the efforts to clone the Huntington's disease locus, are responsible for this phenotype. The second locus maps to chromosome 9 and is syntenic to the mouse deafness (*dn*) locus. The affected children in this family have profound prelingual hearing impairment. Six of 10 children are affected in an extended consanguineous family that has no other phenotypic abnormality. The *dn* locus represents the only known mutation to cause nonsyndromic deafness in mice with no other phenotypic abnormalities. This is a recessive mutant, with degeneration of the organ of Corti, stria vascularis, and occasionally the saccular macula, starting at about 10 days after birth. Investigators in the Laboratory of Molecular Genetics, NIDCD, hypothesize that the gene mapped to chromosome 9 is the human homologue of the gene causing hearing impairment in the *dn* mouse.

Different Mutations Cause Waardenburg Syndrome

Waardenburg syndrome is an inherited disorder characterized by hereditary hearing impairment, one blue eye and one brown eye, and a white forelock. Previous studies showed that point mutations in the *Pax3* gene cause one type of Waardenburg syndrome (Waardenburg syndrome type 1). The second type of Waardenburg syndrome is associated with another mutant gene or genes. Investigators in the Laboratory of Molecular Genetics, NIDCD, identified mutations within the protein coding domain of the *MITF* gene in affected individuals of three families with Waardenburg syndrome type 2 (WS2). Mice homozygous for functionally inactive *mi* genes, which is the mouse homolog of the human *MITF* gene, are depleted of melanocytes. Since melanocytes are critical for inner ear function, it is likely that melanocyte depletion in the inner ear structures is at least part of the pathogenesis of Waardenburg syndrome type 2. These studies identify an important genetic cause of Waardenburg syndrome and provide a major clue regarding the pathogenesis of the hearing impairment associated with this disorder.

Cerebral Function Associated with Language Different in Persons Who Stutter

Chronic developmental stuttering which persists into adulthood has been estimated to affect at least one million persons in the United States and often interferes with social communication and employment. The current therapy is behavioral in nature, in which persons who stutter learn to control symptoms by modification of speech production techniques. While behavioral modification can be helpful in the short run, additional training is usually required throughout adult life, and some patients receive little benefit from the training. The precise nature of the

pathophysiological defect that causes this speech dysfluency remains elusive. Defining the nature of such a defect can be the first step in establishing improved treatment modalities. Investigators in the Neuroimaging Sciences Unit of the Voice, Speech, and Language Branch, NIDCD, completed a large-scale neuroimaging study of brain function in people who stutter. In this study, positron emission tomography (PET) was used to study brain activity in adults who had stuttered since childhood, measuring brain activity during a series of speech and language tasks which were designed to evoke or attenuate stuttering symptoms. Persons who stutter differ markedly in the way they formulate and express language, failing to demonstrate the typical left hemisphere lateralization seen in control subjects during these tasks. Instead, brain activity in stutterers is bilateral or lateralized to the right hemisphere. When the relationship between the severity of stuttering symptoms and functional brain activity is examined, the results suggest that activation of left hemispheric regions may be related to the production of stuttered speech, while activation of right hemispheric regions may represent compensatory processes associated with fluent speech production. Significant differences are detected between groups when all subjects are fluent during both language tasks and simple movements of the lips, tongue, jaw and larynx without language content, demonstrating that cerebral function may be fundamentally different in persons who stutter, even in the absence of stuttering.

Research Management and Support

Integrated Planning and Policy Working Group

Responding to a congressional and administration desire for a thorough examination of research programs at the National Institutes of Health, NIDCD established an integrated planning and policy committee to conduct an in-depth review of its extramural and intramural programs. Pursuant to this, the Integrated Planning and Policy Working Group (IPPWG) was established. The IPPWG, consisting of scientific leaders in the mission areas of the Institute, met in April 1995 to review the Institute's analysis of the extramural and intramural research portfolios and to determine if the representation of scientific disciplines matched the research opportunities in hearing, balance, smell, taste, voice, speech, and language in an advantageous and optimal way. It was determined that the NIDCD portfolios should have additional emphasis in four scientific disciplines: molecular biology, molecular genetics, imaging, and integrative neuroscience.

The Partnership Program

The Partnership Program is a comprehensive minority research and training demonstration program between the NIDCD and four academic institutions. At present, program participants include The Morehouse School of Medicine/Atlanta University Complex, the University of Alaska System, the University of Puerto Rico, and Gallaudet University. These universities have large enrollments of individuals currently underrepresented in biomedical and behavioral research. The Partnership Program is designed to maximize opportunities for underrepresented minority individuals to participate in fundamental and clinical research on hearing, balance, smell, taste, voice, speech, and language. It will also provide support for strengthening of curriculum and current research activities and for the exchange of scientists, students, and administrators.

Budget Policy

In the FY 1997 President's Budget Request, NIDCD support for research project grants (RPGs) would increase by 2.4 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 173 competing RPGs, an increase of 12 competing RPGs over FY 1996, and 603 total RPGs, an increase of 27 total RPGs over FY 1996. A 2.2 percent stipend increase will be provided to NRSA training positions.

The FY 1997 budget request includes \$1,500,000 to support research on nonsyndromic hereditary hearing impairment and \$1,000,000 to support research on development of a vaccine against otitis media.

National Institute on Deafness and Other Communication Disorders

Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects:						
Noncompeting.....	382	\$82,629,000	394	\$85,925,000	409	\$84,398,000
Administrative supplementals.....	(15)	302,000	(16)	274,000	(16)	274,000
Competing projects:						
Renewals.....	67	17,058,000	67	17,765,000	72	19,678,000
New.....	94	12,329,000	93	12,711,000	100	14,092,000
Supplements.....	1	127,000	1	132,000	1	136,000
Subtotal, competing.....	162	29,514,000	161	30,608,000	173	33,906,000
Subtotal, research projects.....	544	112,445,000	555	116,807,000	582	118,578,000
Total, SBIR/STTR.....	18	3,411,000	21	3,297,000	21	4,109,000
Total, RPGs.....	562	115,856,000	576	120,104,000	603	122,687,000
Research Centers:						
Specialized/comprehensive centers.....	16	15,577,000	16	16,531,000	16	17,164,000
Other Research:						
Research career programs.....	32	2,506,000	35	2,968,000	38	3,275,000
Cooperative clinical.....	1	1,262,000	1	1,174,000	1	1,174,000
Minority biomedical support.....	0	165,000	0	576,000	0	576,000
Other research.....	10	460,000	15	733,000	15	733,000
Subtotal, other research.....	43	4,393,000	51	5,451,000	54	5,758,000
Total, research grants.....	621	135,826,000	643	142,086,000	673	145,609,000

Research Training:

Individual awards:					
Noncompeting.....	22	590,000	31	886,000	39
Competing awards.....	29	718,000	20	500,000	12
Subtotal, individual.....	51	1,308,000	51	1,386,000	51
Institutional awards:					
Noncompeting.....	164	3,633,000	154	4,102,000	91
Competing awards.....	31	636,000	41	719,000	104
Subtotal, institutional.....	195	4,269,000	195	4,821,000	195
Total, research training.....	246	5,577,000	246	6,207,000	246
Research and development contracts.....	19	5,762,000	19	7,297,000	19
	FTEs		FTEs		FTEs
Intramural research.....	46	11,646,000	55	11,968,000	55
Research management and support.....	79	8,327,000	79	7,294,000	79
Total.....	125	167,138,000	134	174,852,000	134
Clinical trials.....		(9,427,000)		(10,241,000)	
					(10,495,000)

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Activity

(Dollars in Thousands)

	1993 Actual		1994 Actual		1995 Actual		1996 Estimate		1997 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research												
Deafness and Other Communication Disorders	---	\$137,599	---	\$145,165	---	\$147,109	---	\$155,590	---	\$159,528	---	+\$3,938
Intramural research	44	9,223	45	9,967	45	11,646	55	11,968	55	12,268	---	+300
Research management and support	89	7,215	80	7,540	80	8,327	79	7,294	79	7,294	---	---
Total obligations	133	154,037	125	162,672	125	167,082	134	174,852	134	179,090	---	+\$4,238
Unobligated balance	---	121	---	41	---	56	---	---	---	---	---	---
Total budget authority	133	154,158	125	162,713	125	167,138	134	174,852	134	179,090	---	+\$4,238

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Summary of Changes

1996 Estimated budget authority.....	\$174,852,000
1997 Estimated budget authority.....	179,090,000
Net Change.....	+4,238,000

	1996 Current Estimated Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Research:				
a. Within grade increase.....	---	\$4,987,000	---	+\$45,000
b. Annulization of January 1996 pay increase.....	---	4,987,000	---	+38,000
c. 1997 pay increase.....	---	4,987,000	---	+114,000
d. Payment for centrally furnished services.....	---	1,597,000	---	+147,000
e. Increased cost of service and supply fund.....	---	501,000	---	+14,000
f. Increased cost of materials and other supplies.....	---	5,384,000	---	+104,000
Subtotal.....	---		---	+462,000
2. Research Management and Support:				
a. Within grade Increase.....	---	4,256,000	---	+62,000
b. Annulization of January 1996 pay increase.....	---	4,256,000	---	+33,000
c. 1997 pay increase.....	---	4,256,000	---	+98,000
d. FECA.....	---	4,256,000	---	+2,000
e. Payment for centrally furnished services.....	---	1,913,000	---	-98,000
f. Increased cost of service and supply fund.....	---	259,000	---	+2,000
g. Increased cost of materials and other supplies.....	---	1,125,000	---	+23,000
Subtotal.....	---		---	+122,000

Summary of Changes - Continued

	1996 Current Estimated Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
<u>Changes:</u>				
<u>A. Program:</u>				
1. Research Project Grants				
a. Noncompeting.....	394	\$86,199,000	+15	-\$1,527,000
b. Competing.....	161	30,608,000	+12	+3,298,000
c. SBIR/STTR.....	21	3297000	- - -	+812,000
Subtotal, RPGs.....	- - -			+2,583,000
2. Research Centers.....	16	16,531,000	- - -	+633,000
3. Other Research				
a. Research Career Awards.....	35	2,968,000	- - -	+307,000
b. Cooperative Clinical.....	1	1174000	- - -	- - -
c. Minority Biomedical research supplement.....	- - -	576000	- - -	- - -
d. Other research related.....	15	733000	- - -	- - -
4. Research Training				
a. Individual.....	51	1386000	- - -	+28,000
b. Institutional.....	195	4821000	- - -	+83,000
5. Research and development contracts.....	19	7,297,000	- - -	+304,000
Subtotal, Extramural.....	- - -			+3,938,000
	<u>FTEs</u>		<u>FTEs</u>	
6. Intramural Research.....	55	11,968,000	- - -	-162,000
7. Research Management and Support.....	78	7,294,000	-1	-122,000
Total Changes.....	- - -			+4,238,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment.....	134	134	- - -
Full-time equivalent of overtime and holiday hours.....	.1	.1	- - -
Average SES salary.....	\$117,864	\$120,221	+\$2,357
Average GM/GS grade.....	10	10	- - -
Average GM/GS salary.....	48,030	48,990	+960
Average salary of ungraded positions.....	21,258	21,683	+425
Personnel Compensation:			
Full-time permanent.....	\$4,629,000	\$4,796,000	+\$167,000
Other than full-time permanent.....	1,289,000	1,303,000	+14,000
Other personnel compensation.....	169,000	171,000	+2,000
Special personnel compensation.....	1,740,000	1,821,000	+81,000
Total personnel compensation.....	7,827,000	8,091,000	+264,000
Personnel benefits.....	1,405,000	1,429,000	+24,000
Benefits to former personnel.....	6,000	6,000	- - -
Travel and transportation of persons.....	344,000	350,000	+6,000
Transportation of things.....	50,000	50,000	- - -

	1996 Estimate	1997 Estimate	Increase or Decrease
Rental payment to others.....	\$550,000	\$567,000	+\$17,000
Communications, utilities and miscellaneous charges.....	650,000	651,000	+1,000
Printing and reproduction.....	65,000	65,000	- - -
Other services:			
Consultant Services.....	41,000	41,000	- - -
Other services.....	690,000	662,000	-28,000
Purchases from Govt. accounts.....	2,915,000	2,835,000	-80,000
Operation & Main. of Equipment.....	636,000	656,000	+20,000
Medical Care.....	84,000	88,000	+4,000
Research and Development			
Contracts.....	5,181,000	5,471,000	+290,000
Subsistence & support of persons.....	3,604,000	3,655,000	+51,000
Supplies and materials.....	1,296,000	1,315,000	+19,000
Equipment.....	1,215,000	1,231,000	+16,000
Grants, subsidies & contributions.....	148,293,000	151,927,000	+3,634,000
* Total, budget authority.....	174,852,000	179,090,000	+4,238,000

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Administrative Costs
(BUDGET AUTHORITY)

	1996 Estimate	1997 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)	\$4,629,000	\$4,796,000	167,000
Other than Full-time Permanent (11.3)	1,289,000	1,303,000	14,000
Other Personnel Compensation (11.5)	169,000	171,000	2,000
Special Personnel Services (11.8)	1,740,000	1,821,000	81,000
Total Personnel Compensation (11.9)	7,827,000	8,091,000	264,000
Civilian Personnel Benefits (12.1)	1,405,000	1,429,000	24,000
Benefits to Former Personnel (13.0)	6,000	6,000	- - -
Travel (21.0)	344,000	350,000	6,000
Transportation of Things (22.0)	50,000	50,000	- - -
Rental Payments to Others (23.2)	550,000	567,000	17,000
Communications, Utilities, and Miscellaneous Charges (23.3)	650,000	651,000	1,000
Printing and Reproduction (24.0)	65,000	65,000	- - -
Other Contractual Services			
Advisory and Assistance Services (25.1)	41,000	41,000	- - -
Other Services (25.2)	690,000	662,000	-28,000
Purchases from Govt. Accounts (25.3)	279,000	285,000	6,000
Operation & Maintenance of Facilities (25.4)	- - -	- - -	- - -
Medical Care (25.6)	84,000	88,000	4,000
Operation & Maintenance of Equipment (25.7)	636,000	656,000	20,000
Subsistence & Support of Persons (25.8)	3,604,000	3,655,000	51,000
Supplies and Materials (26.0)	1,296,000	1,315,000	19,000
Total	17,527,000	17,911,000	384,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS
COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Dysphonia - The House in its report 104-209, page 73 states that the NIDCD intramural scientists pioneered the development of a new treatment for spasmodic dysphonia using injections into the laryngeal muscle. The Committee recommends continued NIDCD intramural and extramural study into spasmodic dysphonia.

Action Taken or to be Taken

Laryngeal dystonia, also known as spasmodic dysphonia, has been studied in the NIDCD intramural research program since the Institute was formed in 1989. Current research efforts are exploring the pathophysiologic importance of abnormalities found in a laryngeal sensory reflex arc in patients with spasmodic dysphonia. Research is underway to use neuro-imaging techniques that highlight regions with high brain activity to compare speech and language processing in normal individuals and patients with voice disorders including spasmodic dysphonia. Immediate plans are underway to identify and study families where these voice disorders appear to be inherited in an effort to use gene linkage techniques to map and isolate the genes which predispose individuals to inherited forms of voice disorders.

The NIDCD currently supports a number of extramural research projects within the Voice and Speech Program that are related to the scientific area of dystonia. It is anticipated that the Institute will continue to receive and fund applications that examine dysphonia.

1996 Senate Appropriations Committee Report LanguageItem

Spasmodic dysphonia - ...The Senate in its report 104-145, page 94, states that spasmodic dysphonia is a voice disorder that affects women predominantly, and usually renders a person difficult to understand because of uncontrolled voice and pitch breaks. The committee recommends continued NIDCD intramural and extramural study into spasmodic dysphonia.

Action Taken or to be Taken

Spasmodic dysphonia, has been studied in the NIDCD intramural research program since the

Institute was formed in 1989. Current research efforts are exploring the pathophysiologic importance of abnormalities found in a laryngeal sensory reflex arc in patients with spasmodic dysphonia. Research is underway to use neuro-imaging techniques that highlight regions with high brain activity to compare speech and language processing in normal individuals and patients with voice disorders including spasmodic dysphonia. Immediate plans are underway to identify and study families where these voice disorders appear to be inherited in an effort to use gene linkage techniques to map and isolate the genes which predispose individuals to inherited forms of voice disorders.

The NIDCD currently supports a number of extramural research projects within the Voice and Speech Program that are related to the scientific area of dystonia. It is anticipated that the Institute will continue to receive and fund applications that examine dysphonia.

Item

Partnership program - ...The Senate in its report 104-145, page 94 states that the Committee continues to support the Comprehensive Minority Partnership Program between NIDCD, the University of Puerto Rico, Morehouse School of Medicine, and the University of Alaska system. The Committee encourages NIDCD to provide the resources needed to develop culturally and linguistically sensitive diagnostic and assessment tools for each of the populations served by these institutions and encourages the NIDCD to provide these institutions an opportunity to compete for funding in this area.

Action Taken or to be Taken

The Partnership Program is designed to maximize opportunities for underrepresented minority individuals to participate in fundamental and clinical research on hearing, balance, smell, taste, voice, speech and language. The Program also provides support for strengthening of curriculum and current research activities, and for the exchange of scientists, students, and administrators in order to provide additional opportunities to participate in fundamental and clinical research projects in all areas of human communication. In FY 1995, the Program sponsored 14 individuals, who participated in research projects at the NIDCD in Bethesda. The group represented under-graduate students, post-graduate students, and faculty members. The NIDCD is anticipating that a similar number of students and faculty members will be supported in the future.

In FY 1997, the NIDCD is planning a study which will collect cross-sectional data on language abilities in normally developing 4-6 year olds who speak Black English. Data will be collected in urban, suburban and rural environments within the United States and will document age-appropriate language milestones and behaviors. These data will be used for a language assessment instrument or procedure which could be used to differentiate between language impairment and normal language development. A pilot study validating these language assessment instruments or procedures with children in the targeted language group will be conducted. At the conclusion of this study, the NIDCD plans to conduct a similar study with Hispanic children.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Authorizing Legislation

Funded Authorizations:	PHS Act/ Other Citation	U.S. Code Citation	1996 Amount		1997 Amount Authorized	1997 Budget Request
			Authorized	Estimate		
Research and Investigation.....	Section 301	42§241	Indefinite		Indefinite	
National Institute on Deafness and Other Communication Disorders	Section 464 A-F	42§281	Such sums as necessary	\$168,645,000	Such sums as necessary	\$172,772,000
National Research Service Awards.....	Section 487(d)	42§288	Such sums as necessary	6,207,000	authorization pending	6,318,000
Total Budget Authority			174,852,000		179,090,000	

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation ^{1/}</u>
1989 ^{2/}	---	---	\$87,600,000	\$86,530,000
1990	\$99,902,000	\$99,952,000	121,116,000	118,839,000 ^{3/}
1990 Sequester				-1,256,000
1991	122,847,000	125,623,000 ^{4/}	148,247,000	134,935,000 ^{5/}
1991 Sequester				-2,000
1992	146,321,000	144,495,000	151,106,000	149,102,000 ^{6/}
1993	157,301,000	153,466,000	157,301,000	154,814,000 ^{7/}
1994	153,088,000	162,823,000	162,823,000	162,823,000
1995 ^{8/}	167,129,000	166,155,000	167,129,000	166,761,000
1996	172,399,000 ^{9/}	174,852,000	170,540,000 ^{9/}	174,852,000
1997 ^{9/}	179,090,000			

^{1/} Reflects enacted supplementals, rescissions, and reappropriations.

^{2/} The House allowance excluded funds for the unauthorized training programs (National Research Service Awards). The Senate allowance includes the budget for NRSA's. It included up to \$93,100,000 for establishment of the proposed new National Institute on Deafness and Other Communication Disorders (NIDCD). The appropriation included the budget of the NRSA program and provided up to \$96,100,000 for the establishment of the proposed new institute, NIDCD.

^{3/} Excludes enacted administrative reductions of \$161,000.

^{4/} Excludes \$3,123,000 in NRSA training programs requested but not considered.

^{5/} Excludes the enacted administrative reduction of \$3,562,000.

^{6/} Excludes the enacted administrative reduction of \$1,041,000.

^{7/} Excludes the enacted administrative reduction of \$1,528,000.

^{8/} Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995, FY 1996 and FY 1997.

^{9/} Excludes enacted administrative reductions of \$69,000, \$9,000, and \$47,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Detail of Full-time Equivalent Employment (FTEs)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	8	8	8
Office of Administration.....	37	37	37
Division of Intramural Research.....	46	55	55
Division of Extramural Activities.....	19	19	19
Division of Communication Sciences and Disorders.....	15	15	15
Total, NIDCD.....	125	134	134

Average GS/GM Grade

1990	9.5
1991	9.6
1992	9.6
1993	10.0
1994	10.0
1995	10.0
1996	10.0
1997	10.0

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute on Deafness and Other Communication Disorders

Program Administration
Detail of End of the Year Employment

	1995 Actual	1996 Estimate	1997 Request
Executive level I.....	---	---	---
Executive level II.....	---	---	---
Executive level III.....	---	---	---
Executive level IV.....	---	---	---
Executive level V.....	---	---	---
Subtotal	---	---	---
ES-6.....	---	---	---
ES-5.....	1	1	1
ES-4.....	1	1	1
ES-3.....	---	---	---
ES-2.....	---	---	---
ES-1.....	---	---	---
Subtotal	2	2	2
GS/GM-15	9	10	10
GS/GM-14	15	15	15
GS/GM-13	11	11	11
GS-12	20	22	22
GS-11	8	8	9
GS-10	1	1	1
GS-9	8	10	10
GS-8	7	8	7
GS-7	20	20	20
GS-6	3	3	3
GS-5	---	---	---
GS-4	5	5	5
GS-3	1	1	1
GS-2	---	---	---
GS-1	---	---	---
Subtotal	108	114	114

Grades Established
by Act of July 1, 1994
(42 U.S.C. 207)

Assistant Surgeon General	---	---	---
Director Grade	1	1	1
Senior Grade	---	---	---
Full Grade	1	1	1
Senior Assistant Grade	---	---	---
Assistant Grade	---	---	---
Subtotal	<u>2</u>	<u>2</u>	<u>2</u>
Ungraded	17	19	19
Total Permanent			
Positions	106	114	114
Total Positions End of Year	129	137	137
Total (FTE) End of Year	125	134	134
Average ES level	2	2	2
Average ES salary	115,554	117,864	120,221
Average GS/GM grade	10	10	10
Average GS/GM salary	47,088	48,030	48,990

TUESDAY, APRIL 23, 1996.

OFFICE OF AIDS RESEARCH

WITNESSES

DR. WILLIAM E. PAUL, DIRECTOR, OFFICE OF AIDS RESEARCH

DR. JACK E. WHITESCARVER, DEPUTY DIRECTOR

WENDY J. WERTHEIMER, SENIOR ADVISOR

DONNA D. ADDERLY, SENIOR BUDGET ANALYST, OFFICE OF FINANCIAL MANAGEMENT

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. Next we are pleased to welcome Dr. William Paul, the director of the Office of AIDS Research.

Dr. Paul, if you would introduce the people with you and then proceed with your testimony, we would appreciate it.

INTRODUCTION OF WITNESSES

Dr. PAUL. Thank you, Mr. Porter.

On my far left is Ms. Donna Adderly, our budget analyst; Ms. Wendy Wertheimer, senior advisor; and Dr. Jack Whitescarver, the deputy director of the Office of AIDS Research. And, of course, we hardly need introduce Dr. Harold Varmus or Mr. Dennis Williams, but it is always a pleasure, nonetheless, to have them with us at this table.

OPENING STATEMENT

Mr. Chairman and Members of the subcommittee, I am pleased to speak to you today about the NIH research program to combat the most critical public health emergency of our lifetime, HIV and AIDS, and about the leadership of the Office of AIDS Research in this effort.

AIDS has had a devastating impact on our Nation. In the 15 years since the disease was first identified, it has risen to be the number one killer of young Americans. Far from being confined to a single group, the AIDS epidemic is dynamic and is moving into new populations, increasingly involving women and disproportionately affecting persons from racial and ethnic minorities.

AIDS cases resulting from heterosexual transmission have dramatically increased.

Outside the United States, the situation is even more dire. The World Health Organization estimates that nearly 20 million adults and children have already become HIV infected, and that more than two-and-a-half million have died.

Nearly 10,000 new infections occur each day.

Congress has provided both the funding and the legislative authority to allow the Nation to make a remarkable research commitment, leading the world in the effort to confront this global emergency. It is the role of the Office of AIDS Research to plan, coordinate, and evaluate the NIH AIDS research effort, assuring that we attack the disease comprehensively and setting in place overall scientific direction and priority.

America's substantial investment in AIDS research is now reaping benefits and providing new and exciting scientific opportunities. Advances in our understanding of the genes and proteins of the human immuno-deficiency virus have allowed the development of increasingly effective anti-retroviral drugs. Eight such drugs are currently approved for the treatment of HIV infection.

The administration of AZT, in combination with other anti-retroviral drugs has been shown to extend life in HIV-infected individuals.

Early results from studies conducted by pharmaceutical companies with an exciting new class of drugs, protease inhibitors, are very encouraging. When used with other anti-retroviral drugs, protease inhibitors can suppress virus levels 100 to 1,000 fold, or even more, for extended period of time.

We have made significant advances in the treatment and prevention of opportunistic infections associated with AIDS, prolonging the lives of HIV-infected people, and improving their quality of life.

NIH achieved a landmark success in demonstrating that, with the use of AZT, HIV transmission from mother to infant can be prevented in two-thirds of individuals. As a result, the virtual elimination of mother-to-child transmission of HIV in the United States is an objective that we can set with true hope of achievement.

At the same time, we remain very far from attaining our dual goals of finding durable treatments against HIV and its associated illnesses for those who are already infected, and for developing vaccines and other methods to prevent infection for the many millions more who are at risk.

Better anti-retroviral drugs and effective treatments to restore immune function are urgently needed. A preventive vaccine, our greatest hope for the eradication of AIDS, remains an illusive but not unattainable goal. Better understanding of human behavior and behavior change is necessary to develop effective techniques to prevent infection.

The development of topical microbicides would provide women with a method of protection from sexual transmission. Indeed, we have much more to learn about the course of the infection in women and about preventing and treating the complications unique to or more prevalent in women.

The magnitude and complexity of these challenges have made the NIH AIDS research program unique. AIDS research transcends every area of clinical medicine and scientific investigation, crossing the boundaries of every NIH institute and center.

The role of the OAR is to identify areas of greater scientific need and promise, to assure that resources are directed to those areas, and to ensure collaboration and minimized duplication in a united research front against the epidemic.

To carry out its mandate, the OAR has spearheaded two important initiatives: the development of a trans-NIH research plan and budget, and a recently-completed comprehensive evaluation.

The hallmark of each of the activities of the OAR, and particularly these two critical endeavors, is the central participation of the scientific community. At every level of these planning and evaluation processes, the OAR has convened groups of eminent scientists from across America and the world, including Nobel laureates and members of the National Academy of Sciences, to forge scientific consensus on future directions and priorities for research.

When I became OAR director, I realized that planning and budgeting for the future of NIH AIDS research would only be possible with a frank and thorough evaluation of our existing programs and an assessment of where new opportunities lie. Indeed, AIDS research has reached a turning point, requiring new strategies and directions to capitalize on our recent achievements and to respond to the changing epidemic.

The OAR's Advisory Council reached the same conclusion and convened a group to undertake a review unprecedented in its scope.

Dr. Arnold Levine of Princeton University was asked to assemble and lead a group of scientific experts from outside Government to evaluate each of the components of the current AIDS research program. The group was asked to take a broad view in assessing how these components fit together and whether, as a whole, the program is moving effectively and efficiently toward the goal of preventing and curing AIDS.

This group of distinguished scientists assessed all NIH-sponsored AIDS research. Their report provides a blueprint for restructuring the AIDS research program, to streamline research, strengthen high-quality programs, eliminate inadequate ones, and to ensure that the American people reap the full benefits of their substantial investment in AIDS research.

This report, copies of which we have provided, makes a series of far-reaching recommendations. It acknowledges that, although much of the NIH AIDS research portfolio was of the highest quality and relevance, changes are necessary at this time. Certain programs that are no longer making the contributions for which they were designed can be refocused or terminated. Others need to be reorganized to more effectively deal with the challenges we now face. In still other instances, entirely new programs are needed.

Some of the key recommendations of the report are that the NIH should dramatically increase support for investigator-initiated research; restructure and strengthen the AIDS vaccine research effort, and place particular emphasis on gaining a fuller understanding of the human immune system; develop a comprehensive HIV prevention science agenda; and integrate all adult clinical trials programs into a single network. We believe that this report provides a framework for a comprehensive and reinvigorated scientific assault on AIDS.

The OAR, the NIH director, and the directors of the NIH institutes and centers are now developing strategies for the implementation of these recommendations.

To set this process in motion as quickly as possible, the OAR has committed its discretionary funds for fiscal year 1996 toward the

first goal of increasing support for unsolicited investigator-initiated research. The consolidated appropriation for AIDS research in the President's request will provide the NIH the flexibility to more fully put the report's recommendations and priorities into effect in the coming fiscal year.

AIDS is paradoxically both a unique challenge and a prototype for other epidemics that surely lie ahead. Our actions will have a lasting impact on our ability to confront what a recent book calls "the coming plagues." Complacency now is not an option. We must work faster and more efficiently, utilizing our precious resources where they will be most effective, with clear scientific priorities and direction.

The OAR requests a consolidated appropriation of \$1,431,908,000 for AIDS and AIDS-related research at the National Institutes of Health. Such an appropriation will permit the strengthening and refocusing of the NIH AIDS research effort toward achieving our ultimate goal: preventing and curing AIDS.

I will be pleased to answer any questions you may have.

[The prepared statement of Dr. William Paul follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
Office of AIDS Research

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Outside the U.S. the situation is even more dire. The World Health Organization estimates that nearly 20 million adults and children have already become HIV-infected and more than 2.5 million adults, children, and infants have died. Nearly 10,000 new infections occur each day.

Congress has provided both the funding and the legislative authority to allow the nation to make a remarkable research commitment, leading the world in the effort to confront this global emergency. It is the role of the Office of AIDS Research to plan, coordinate, and evaluate the NIH AIDS research effort, assuring that we attack the disease comprehensively, and setting in place overall scientific direction and priorities.

America's substantial investment in AIDS research is now reaping benefits and providing new and exciting scientific opportunities. Breakthroughs in our understanding of the genes and proteins of the human immunodeficiency virus have allowed the development of increasingly effective anti-retroviral drugs. Eight such drugs are currently approved for the treatment of HIV infection. The administration of AZT in combination with other antiretroviral drugs has been shown to extend life in HIV-infected individuals. Early results from studies conducted by pharmaceutical companies with an exciting new class of drugs, the protease inhibitors, are very encouraging. When used with other antiretroviral drugs, protease inhibitors can suppress virus levels 100- to 1000-fold or even more for extended periods of time.

We have made significant advances in the treatment and prevention of opportunistic infections associated with AIDS, extending the lives of HIV-infected individuals and improving their quality of life.

NIH achieved a landmark success in demonstrating that, with the use of AZT, HIV transmission from mother to infant can be prevented in two-thirds of individuals. As a result, the virtual elimination of mother-to-child transmission of HIV in the U.S. is a goal that we can set with true hope of achievement.

At the same time, we remain very far from attaining our dual goals of finding durable treatments against HIV and its associated illnesses for those who are already infected and developing vaccines and other methods to prevent infection for the many millions more who are at risk. Better antiretroviral drugs and effective treatments to restore immune function are urgently needed. A preventive vaccine, our greatest hope for the eradication of AIDS, remains an elusive but not unattainable goal. A better understanding of human behavior and behavior change is necessary to develop effective techniques to prevent infection. The development of topical microbicides would provide women with a method of protection from sexual transmission. We have much more to learn about the course of the infection in women and about preventing and treating the complications unique to or more prevalent in women. We have not determined how HIV actually causes destruction of the immune system and subsequent illness.

The magnitude and complexity of these challenges have made the NIH AIDS research program unique. AIDS research transcends every area of clinical medicine and scientific investigation, crossing the boundaries of every NIH institute and center. The role of the Office of AIDS Research is to identify areas of greatest scientific need and promise, to assure that resources are directed to those areas, and to ensure collaboration and minimize duplication in a united research front against the epidemic.

To carry out its mandate, the Office of AIDS Research has spearheaded two important initiatives: the development of an annual trans-NIH research plan and budget and a recently completed comprehensive evaluation. The hallmark of each of the activities of the Office of AIDS Research, and particularly these two critical endeavors, is the central participation of the scientific community. At every level of these planning and evaluation processes, the Office of AIDS Research has convened groups of eminent scientists from across America and the world, including Nobel laureates and members of the National Academy of Sciences, to forge scientific consensus on future directions and priorities for research.

When I became Director of the Office of AIDS Research, I realized that planning and budgeting for the future of NIH AIDS research would only be possible with a frank and thorough evaluation of our existing programs and an assessment of where new opportunities lie. Indeed, AIDS research has reached a turning point, requiring new strategies and directions to capitalize on our recent achievements and to respond to the changing epidemic.

The Office of AIDS Research Advisory Council reached the same conclusion and convened a group to undertake a review unprecedented in its breadth and scope.

Dr. Arnold Levine of Princeton University was asked to assemble and lead a group of scientific experts from outside government to evaluate each of the components of the current NIH AIDS research program. The group was asked to take a broad view in assessing how these components fit together and whether as a whole the program is moving effectively and efficiently toward the goal of preventing and curing AIDS.

This group of distinguished scientists and experts assessed all NIH-sponsored AIDS research to assure that the most promising areas of science are being supported, that the critical scientific questions are being addressed, and that the most effective use is being made of federal AIDS research resources. Their report provides a blueprint for restructuring the NIH AIDS research program to streamline research, strengthen high-quality programs, eliminate inadequate programs, and ensure that the American people reap the full benefits of their substantial investment in AIDS research.

Their report, copies of which we have provided, makes a series of far-reaching recommendations. It acknowledges that although much of the NIH AIDS research portfolio is of the highest quality and relevance, changes are necessary at this time. Certain programs which are no longer making the contributions for which they were designed can be refocused or terminated. Others need to be reorganized to more effectively deal with the challenges we now face. In still other instances, entirely new programs are needed.

Some of the key recommendations of the report are that the NIH should:

- Dramatically increase support for investigator-initiated research;
- Restructure and strengthen the NIH AIDS vaccine research effort-- with particular emphasis on understanding the human immune system;
- Develop a comprehensive NIH HIV prevention science agenda;
- Integrate all adult clinical trial programs into a single network.

We believe that this report provides a framework for a comprehensive and reinvigorated scientific assault on AIDS. The Office of AIDS Research, the Director of NIH and the Directors of the NIH Institutes and Centers, are now developing strategies for the implementation of these recommendations.

To set this process in motion as quickly as possible, the Office of AIDS Research has committed its discretionary funds for FY 1996 toward the first goal of increasing support for unsolicited investigator-initiated research. The consolidated appropriation for AIDS research in the President's request will provide the NIH the flexibility to put the report's recommendations and priorities into effect within the coming fiscal year.

AIDS is, paradoxically, both a unique challenge and a prototype for other epidemics that surely lie ahead. Our actions will have a lasting impact on our ability to confront what a recent book calls "the coming plagues". Complacency now is not an option. We must work faster and more efficiently, utilizing our precious resources where they will be most effective, with clear scientific priorities and direction.

The Office of AIDS Research requests a consolidated appropriation of \$1,431,908,000 for NIH AIDS and AIDS-related research. Such an appropriation will permit the strengthening and refocusing of NIH AIDS research effort toward achieving our ultimate goal--preventing and curing AIDS. I will be pleased to answer any questions you may have.

OVERALL BUDGET INCREASE

Mr. PORTER. Thank you, Dr. Paul. That would represent a 1.7-percent increase over last year's funding; is that correct?

Dr. PAUL. That is correct.

HIV TRANSMISSION

Mr. PORTER. I wonder if you could begin by telling us—and I think we know the answers to these questions, but I want to go into some depth on them. What are the most usual methods of HIV transmission? Is it homosexual, unprotected sex? Heterosexual, unprotected sex? The use of needles, needle sharing among drug users? Why don't you give us some understanding.

Dr. PAUL. Within the United States?

Mr. PORTER. Yes, within the United States.

Dr. PAUL. The shape of the current epidemic, is such that the acquisition of HIV infection through homosexual transmission has now fallen to account for somewhat less than half of the new cases.

Injecting drug use is becoming an increasingly important aspect of the transmission.

But, finally, heterosexual transmission now has risen to account for a substantial fraction of the number of cases within the U.S.

Mr. PORTER. What fraction is that?

Dr. PAUL. I think that percentage is of the order of 13 percent.

Mr. PORTER. It's 13 percent, and homosexual is how much?

Dr. PAUL. I believe the current numbers are slightly under 50 percent, but I would have to check that to be absolutely certain. I think that is correct, sir.

I should also point out——

Mr. PORTER. Now drug use would then be——

Dr. PAUL. Of the order——

Mr. PORTER. 39 percent?

[CLERK'S NOTE.—Subsequent to the hearing OAR changed this figure to "31 percent".]

Dr. PAUL. Something of the order of 37 percent. I will provide you with precise numbers for the record, sir.

[The information follows:]

AIDS CASES BY EXPOSURE CATEGORY IN 1995 IN THE UNITED STATES CITED IN THE CDC "HIV/AIDS SURVEILLANCE REPORT" (Vol. 7, No. 2) 1995

Adult/adolescent exposure category	1995	
	Number	Percent
Men who have sex with men	30,671	42
Injecting drug use	19,261	26
Men who have sex with men and inject drugs	3,425	5
Hemophilia/coagulation disorder	445	1
Heterosexual contact	8,093	11
Receipt of blood transfusion, blood components, or tissue	664	1
Other/risk not reported or identified	10,821	15
Adult/adolescent total	73,380	100

¹ No risk reported or identified—cases are in persons with no reported history of exposure to HIV through any of the routes listed in the hierarchy of exposure categories. Risk not identified cases includes persons who are currently under investigation by local health officials, persons whose exposure history is incomplete because they died, declined to be interviewed or were lost to follow-up; and persons who were interviewed or for whom other follow-up information was available and no exposure mode was identified. Persons who have an exposure mode identified at the time of follow-up are reclassified into the appropriate category.

HIV TRANSMISSABILITY

Mr. PORTER. Now, let me ask also, first, for non-minority, because you said there was a difference, in your testimony, between minority and non-minorities in these areas, or perhaps that only applies to certain of these, but could you tell me, for example, what would be the chances of transmission between an HIV-infected person and a non-HIV-infected person for unprotected, heterosexual sex?

Dr. PAUL. Is the question how many individual encounters would be needed?

Mr. PORTER. Yes. Is the chance 1 in 100 or 1 in 5 or 1 in 3?

Dr. PAUL. The difficulty with trying to provide that answer, sir, is that it very much depends upon the status of the partner in that sexual couple who is infected.

For example, an individual who has been recently infected with virus and is going through a phase in which the virus is replicating very rapidly and is reaching exceedingly high levels in their blood and tissues will also have very high levels of virus in semen. That individual is probably more likely to transmit the virus, because the burden or the amount of virus to which the other partner would be exposed would be very high.

By contrast, an individual being treated with one of the new protease inhibitors, together with reverse transcriptase inhibitors, may have levels of virus in their body and blood that are low enough that we will be barely able to detect them.

And while we have not precisely demonstrated an absolutely precise relationship between viral burden and transmissibility, we can be certain that, with these vastly-different viral burdens, the risk of transmission will be very different.

So it is, therefore, very difficult to say what any individual encounter will carry as its risk. Indeed, I think that makes our responsibility to counsel individuals to not engage in unprotected sex all the more important because it is not simply saying, "Well, there is only 1 in 100 chance that I am at risk from this encounter." It could be that that individual will be in an encounter with a very substantially higher risk.

So I hesitate to give a number, sir, because I fear it might be quite misleading.

Mr. PORTER. All right. I can understand that.

Now, for drug users, if you had someone who was at the stage of HIV infection where the risk was high, the use of a needle would be very likely to pass, because you're going blood-to-blood?

Dr. PAUL. Yes. Again, I would suspect, of course, that will be dependent, to a large degree, on the volume of blood that will be in that needle. There are variables, of course, that again make it very dangerous to try to cite a precise number, a precise likelihood that an individual experience will lead to an infection.

Mr. PORTER. Is there any difference between unprotected homosexual sex and unprotected heterosexual sex with a person that is infected in the way you've described, as far as transmission to the partner?

Dr. PAUL. Well, sir, the mechanical aspects of sex do have a difference. The rectal tissue is substantially more friable and there is a greater risk of injury in the time of sexual encounter, and that

inevitably will increase the likelihood that the virus will penetrate the mucosa.—

Mr. PORTER. So it's more likely that homosexual sex would transmit in that case than heterosexual sex?

Dr. PAUL. I think that is a reasonable conclusion.

Mr. PORTER. And why is heterosexual transmission increasing? What are the major reasons for that?

Dr. PAUL. I think as the pool of infected individuals rises, and since heterosexual sex is, of course, a much more dominant mode in the U.S., there will be larger and larger numbers of cases transmitted in that way.

It should also be pointed out that outside of the United States in many parts of the world heterosexual transmission is clearly the dominant mode of transmission. That appears to be true in many areas of the Caribbean, sub-Saharan Africa, and Asia.

So the situation we have observed here in the U.S. may simply reflect a passing phase of the epidemic rather than a stable property of how we will encounter this infection and this disease in the United States.

Mr. PORTER. Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

VETERANS ADMINISTRATION AND HIV

Dr. Paul, I just left a VA-HUD Appropriations Subcommittee hearing in the room next door where we had the Secretary of the Veterans' Administration before us. In asking him questions relative to AIDS research program, the Secretary stated that the Veterans' Administration hospitals have the highest concentration of AIDS patients of any institutions in America. Were you aware of that?

Dr. PAUL. Sir, I have to admit I'm not, but I have no reason to doubt the statement. We, of course—I'll go home immediately and refresh my memory on that point, sir.

Mr. STOKES. I too was surprised to learn about that situation.

I was going to pose some questions to you relative to that information if you were familiar with the fact, but I'll withhold on that.

Dr. PAUL. Well, I may make one comment, if I can, on that subject, sir.

We have recently undertaken, at the President's request, an effort to prepare a Government-wide AIDS research plan, and, of course, the Veterans' Administration has been a major participant in that effort.

So, while I can't precisely answer the question, I can tell you that their contributions in this area certainly would be ones that we value and regard as important.

HIV IN MINORITY COMMUNITIES

Mr. STOKES. Sure, I understand. This morning Dr. Fauci was here and during that hearing, we discussed the fact that, while African Americans are approximately 12.5 percent of the American population, they represent about 35 percent of the total population in terms of AIDS. Is that of concern to you and your commission?

Dr. PAUL. Certainly, sir. In fact, I fear the numbers are somewhat worse than that, because among new infections the rates

among our black citizens are somewhat higher than that. And certainly in other areas—amongst children born with infection, minority infants make up the vast majority of new cases. We believe that is a terrible problem, sir.

Mr. STOKES. What do you think we can do about it?

Dr. PAUL. Well, I think, of course, the best thing we could do would be to interrupt the transmission of this virus; that is, to spare all of our citizens of this burden. That would be, by far, our best action.

We believe that vaccines and the drugs that the pharmaceutical industry is developing would be valuable for all of our citizens. I think that our first responsibility is to find truly effective means to spare us all of this terrible, terrible burden.

PROSPECTS FOR A VACCINE

Mr. STOKES. Doctor, how far do you think we are away from a vaccine?

Dr. PAUL. Well, this is an area, of course, in which I personally have a special interest. My history in science is as an immunologist. I have worked my whole career on the subject of the immune response.

As you probably know, we came close to conducting a large-scale efficacy trial two years ago with an initial first-generation product. The prevailing scientific judgment was that the scientific data did not support going forward at that time.

There is another product now that is in the earlier phases of evaluation that we believe has a greater likelihood of inducing the two arms of the immune system, which would make this vaccine more likely to be effective, but I think it would be premature to make any judgments about it.

I will not try to give you a date, because I think I will certainly prove to be a very poor prophet were I to do so. I would simply say that I believe the progress that has been made in the understanding of the immune system and the new tools that have been developed, particularly with the development of cytokines that we have learned about in the last decade, give us tools and strategies that have not yet been adequately brought to bear on this problem.

While I am very reluctant to give you a date or a time, I am very much an individual who believes a vaccine is not only possible but is—well, it's certainly essential, and I believe it to be really possible.

Mr. STOKES. Thank you very much, Dr. Paul. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Mr. Istook.

Mr. ISTOOK. Thank you, Mr. Chairman, Dr. Paul.

DISEASE STATISTICS

I have just been looking over some of the things—the CDC report of last November, Dr. Fauci's report from the National Office of Allergy and Infectious Diseases. Would they be the most recent sources of the information about the different statistical breakdowns of different groups and which groups are up and which

groups are down? Or do you have any later information that would not be reflected in their studies?

Dr. PAUL. We rely on data from the CDC. They are the group that provides this information for the Nation, so their data would surely be the best data available, sir.

Mr. ISTOOK. Okay. I just want to understand who to listen to and, of course, make the analysis from the same set of data.

Dr. PAUL. Right.

SUCCESS RATES FOR AIDS RESEARCH

Mr. ISTOOK. In the research on AIDS, can you give us some idea of the ratio of how many research grant applications you receive compared to how many are actually granted? And I guess that's not just numerically, but in terms of the dollars requested and the dollars granted, as well.

Dr. PAUL. Well, the NIH uses, as its measurement for the likelihood of a grant being funded, a so-called "success rate," which reflects the likelihood of a grant being funded over its lifetime, since grants may be resubmitted.

That number is higher than the number you may often hear of, which is often referred to as the "pay line" or the "percentile," because sometimes a grant may be resubmitted.

We fund AIDS research through every institute. I don't have the precise numbers with me at this moment, and I will provide them for the record.

[The information follows:]

For most Institutes and Center (ICs), AIDS grants constitute a very small portion of the competing research project grant (RPG) portfolio which is not statistically significant when calculating success rates. Thus, NIH reports the same success rates for AIDS competing RPGs as for the total success rates for each IC. The National Institute of Allergy and Infectious Diseases is the only exception, because of their large portfolio of AIDS grants, as reflected on the attached table. Success rates for FY 1995-FY 1997 by IC, are displayed below:

NATIONAL INSTITUTES OF HEALTH
Competing Research Projects
Success Rates
TOTAL

	FY 1995 Budget Authority			FY 1996 Estimate			FY 1997 Estimate		
	New	Renewal	Total	New	Renewal	Total	New	Renewal	Total
NCI	21%	44%	26%	20%	54%	26%	18%	47%	22%
NHLBI	22%	39%	27%	17%	44%	22%	17%	43%	23%
NIDR	24%	44%	28%	18%	39%	22%	20%	40%	24%
NIDDK	20%	42%	26%	13%	40%	19%	17%	48%	25%
NINDS	24%	48%	31%	14%	48%	23%	16%	43%	23%
NIAID	19%	43%	25%	19%	40%	25%	17%	35%	22%
(AIDS Only)	(31%)	(36%)	(40%)	(17%)	(35%)	(22%)	(19%)	(35%)	(24%)
NIGMS	25%	58%	39%	23%	57%	34%	21%	52%	31%
NICHD	15%	26%	18%	14%	29%	17%	14%	28%	17%
NEI	28%	45%	36%	40%	31%	35%	46%	31%	39%
NIEHS	11%	38%	16%	20%	27%	22%	22%	33%	25%
NIA	25%	41%	29%	28%	53%	33%	24%	46%	28%
NIAMS	19%	37%	24%	19%	38%	24%	17%	38%	22%
NIDCD	29%	46%	34%	23%	44%	29%	23%	49%	29%
NIMH	15%	40%	19%	14%	34%	17%	14%	32%	18%
NIDA	25%	47%	30%	19%	42%	23%	21%	28%	23%
NIAAA	19%	35%	22%	15%	37%	18%	12%	36%	15%
NINR	32%	38%	32%	19%	55%	21%	25%	64%	27%
NCRR	18%	55%	23%	44%	60%	46%	46%	60%	49%
NCHGR	26%	21%	26%	30%	21%	28%	38%	21%	33%
FIC	64%	75%	65%	28%	75%	32%	26%	55%	28%
TOTAL	21%	44%	27%	18%	44%	24%	18%	41%	23%

Dr. PAUL. But at the very least, in the National Institute of Allergy and Infectious Diseases, which funds the largest proportion of those grants, I believe the success rate is probably in the mid 20 percent.

Mr. ISTOOK. Okay. And to make sure I'm understanding correctly, within this context the success rate is basically the success rate of successful applicants?

Dr. PAUL. For an individual submitting a grant, the chance that that grant will be funded over its life. For example, that grant may not be funded in its first attempt, and the reviewers may recommend certain changes which would increase its score and likelihood of funding. Usually that will be taken into account in the calculation of success rate.

Mr. ISTOOK. How does that compare with the success rate for studies oriented toward other diseases?

Dr. PAUL. Again, we vary from institute to institute.

Mr. ISTOOK. Yes.

Dr. PAUL. Within NIAID, success rates for AIDS and non-AIDS grants are relatively comparable, sir.

Mr. ISTOOK. When you say relatively comparable——

Dr. PAUL. Within a few percent of one another. Yes, I would say within statistical variation.

IMPACT OF CHANGING DEMOGRAPHICS ON RESEARCH

Mr. ISTOOK. Okay. Has the thrust of AIDS research been rechanneled or changed in any way to reflect the different demographics that we were referring to before?

Dr. PAUL. First it must be said that there has been a growing awareness of the fact that we need to be certain that our clinical trials program takes true cognizance of the nature of the changing dynamic of the epidemic. NIH has worked to be certain that we involve appropriate minority groups and women in trials to adequately assess the effect of these agents and the nature of the disease on these groups. Surely we have succeeded in that effort, at least in our largest clinical trials program, the AIDS clinical trials group, where the representation of these groups very much mirrors their proportional representation in the epidemic.

EPIDEMIC VERSUS ENDEMIC

Mr. ISTOOK. I want to make sure I understand correctly. What's the definition that's employed of "epidemic" in this case? It's a term we can all loosely use. I just want to understand what's the operating definition.

Dr. PAUL. You mean why do we refer to this as an epidemic rather than——

Mr. ISTOOK. Yes.

Dr. PAUL. Well, it is an infectious disease in a population which is occurring in proportions that are not historically stable. A disease that has a stable rate would be considered endemic. I know that many have pointed out that the actual numbers of new cases of AIDS in the last several years appears to be stabilizing, and I must say for that I am exceedingly grateful.

Mr. ISTOOK. And even declining in some.

Dr. PAUL. Yes. I think that's a matter of some discussion, and I know you have paid careful attention to these statistics and in a very sophisticated way.

But I think the appropriate way to consider this issue, sir, is to consider that the HIV virus has been interacting with human populations for only a matter of some 15 or 20 years. When we consider that influenza, or smallpox, or polio virus have been interacting with human populations for millennia or more, it seems quite justified to speak of this moment of time in the interaction of humans and this virus as one that clearly describes the properties of an epidemic.

Mr. ISTOOK. So, if I understood you correctly, you're saying the definition usually employed is when it is over its historical levels, which presumes an historical pace, but it's that. So at some point if a disease is declining it might no longer be categorized as epidemic, though, of course, it's—the threat from it remains very real.

Dr. PAUL. I would not disagree with you at all, sir. That is, if an infectious disease remains at a certain level within a population, it is often referred to as "endemic." I personally believe that it would be far too soon, I fear, to classify HIV and AIDS as endemic within our society.

Again, pointing to the fact that we're dealing with such a short evolutionary history, we would be making a serious error in our responsibilities to those who will follow us if we do not take every opportunity to deal with this disease as soon as we can.

Mr. ISTOOK. One final question. Over what period of time do you think it would be necessary to have a steady decline or lowering evidence before it would change from epidemic to endemic?

Dr. PAUL. I have not given that serious thought, sir. I think it's an interesting question.

If I were confident, if I could come to this committee in true confidence and say, "We haven't been able to solve this problem, but we now have confidence that we will have no more than the following number of cases per year into the foreseeable future," even if that were a much higher number than I would like, I would agree that the term "endemic" would be appropriate. I cannot say that to you, sir.

Mr. ISTOOK. Thank you. Thank you, Mr. Chairman.

Mr. PORTER. Mrs. Lowey.

SINGLE NETWORK FOR CLINICAL TRIALS

Mrs. LOWEY. I want to commend Dr. Varmus and Dr. Paul for convening an unprecedented review of the NIH. The review led by Dr. Levine of Princeton is the one I'm referring to, of course. Among the many findings of this panel was that the adult clinical trial programs testing AIDS drugs should be combined into a single network.

Can you comment further on this finding, and specifically: how would it impact funding for the AIDS clinical trial unit and the Terry Beirn trial? And if these trials were combined, could more resources be made available to study AIDS treatment for low income patients, particularly in women and HIV drug users who have particular complications such as TB?

In New York, the epidemic is moving into these populations, and I'm concerned that we spend sufficient funds in studying the appropriate treatment for these people.

Dr. PAUL. I'm very sensitive to your concerns, Mrs. Lowey. The group took the position that the organization of the various clinical trials networks, of which there are many, into a single entity would be aimed not so much to phase out any aspect of that, but rather to organize these entities in such a way that they would work more smoothly together. Trials would be designed in such a way that maximum utility would be gained from the trial.

But it envisaged that such a network would have to continue to include centers that were very much like our AIDS Clinical Trial Units in our academic health centers, and centers that were like those in the Community Programs for Clinical Research on AIDS. All of these centers would be an integral part of this program.

The notion here was, however, we would try to have an integrated leadership, not so much to have a monopoly, but to be certain that they were attacking problems in an effective manner.

One would hope that there would be efficiencies generated from such an event, and, of course, such efficiencies would make possible more studies.

So I would certainly hope that our common goals could be achieved by this approach.

Mrs. LOWEY. Thank you. Thank you, Mr. Chairman.

Mr. PORTER. Mr. Miller.

SBIR SET-ASIDE

Mr. MILLER. Let me ask a couple questions. I'm not sure if you've got the same page I'm on. I'd like to ask a couple questions on this AIDS budget by mechanism. It's page 190 in my book, but I'm not sure where it's for you. What I'm going to ask about is, the summary of the \$1.4 billion.

Dr. PAUL. Sure.

Mr. MILLER. For research projects, there is a total of \$733 million. Okay. The small business set-aside is \$21 million, which is a rather large increase. Could you comment on what that is and how that operates? I think it may be outside our jurisdiction, but—

Dr. PAUL. We are mandated to expend a certain fraction of our resources into the Small Business Innovative Research Program/Small Business Technology Transfer Program and I believe that fraction has escalated so that for fiscal year 1997 I think it's on the order of 2.5 percent, and that's an increase from the prior year.

So this use of the SBIR mechanism is, one that is in response to legislative direction.

Mr. MILLER. That's the \$21 million? Is that what it is?

Dr. PAUL. That is correct.

Dr. VARMUS. That's 2.5 percent NIH-wide. It would be slightly higher in the AIDS category.

Mr. MILLER. Further on down there's something called "research and development contracts, \$266 million." That's nothing to do with small business?

Dr. PAUL. No. Those are mechanisms through which the various institutes achieve certain purposes that are better done through a

contract mechanism than through a grant mechanism. But many of those contracts will be with the universities.

PEER-REVIEWED RESEARCH

Mr. MILLER. Of the \$733 million, the only set-aside that we have of research is that SBIR. The rest is all peer review and things like that?

Dr. PAUL. Yes. In fact, the small business program is, itself, peer reviewed, so all of these resources are peer reviewed. They use a slightly different peer review mechanism, but these funds are entirely peer reviewed.

Mr. MILLER. How much of that goes to academic?

Dr. PAUL. The vast majority of this would go to universities, medical schools, research institutes. I would say—

Mr. MILLER. Small business? How about small business?

Dr. PAUL. Small business would, I suspect, be largely made up of the SBIR program.

ROLE OF SBIR SET-ASIDE

Mr. MILLER. Is that—to put you on the spot, is that the best, most effective use of our dollars in AIDS research, that small business set-aside?

Dr. PAUL. Well, it's difficult to say. Some have been concerned that some—a fraction of the SBIR grants may not meet the same standards that we impose upon our academic health centers. I haven't reviewed in detail the current set of applications. I'd be a little reluctant to make a strong statement on this point.

I should say, however, that in our field, in particular, there is no doubt that a public/private partnership is a very important thing. Biotechnology firms often offer some of the most creative approaches. Unfortunately, these organizations are often under-capitalized. And I would be reluctant to say that the use of this mechanism is not a wise one.

I think the percentage number that has been imposed upon us may be not a wise approach, but the notion that we should be carrying out such interactions I think is a good one.

Mr. MILLER. I agree with the concept. I have concerns that we're setting aside something that may or may not be the best use of \$21 million, and it's a rather large increase. You're only asking for a \$24 million increase this year, and \$5 million of it goes in that area. And you have no choice.

Dr. PAUL. Yes. That's correct, sir. And I—

Mr. MILLER. And that applies to all your institutes; is that right?

Dr. PAUL. That's correct.

Mr. MILLER. So of the total NIH budget—

Dr. VARMUS. NIH-wide we have a \$40 million increase in the SBIR for this year out of a non-buildings and facilities increase of about \$160 million—very appreciable.

Mr. MILLER. Yes. This was, I guess, because of laws that were passed. It was before my time, and I don't understand it, but I guess this applies to all Government contracting in every area, whether it's Defense or anything, I guess.

Dr. VARMUS. I don't know which agencies, but it is trans-agency legislation.

Mr. MILLER. It doesn't seem like it fits into basic research. If you want the best research, you shouldn't set aside—

Dr. VARMUS. Well, there is in fact, a good deal of fundamental research. We do applied research, as well. There are certainly highly-beneficial grant applications that we receive, especially from the small businesses where there are new investigators who have innovative ideas that are very frequently efficiently translated into product development at later stages through the SBIR mechanism. We don't have any strong objection to the principle, but we are concerned about the rapid escalation, especially in a year when our budgetary request from the President is constrained.

Mr. MILLER. Mr. Chairman, we don't have a chance—we can't adjust that number, can we?

Mr. PORTER. I'm sorry. I was—

Mr. MILLER. The small business set-aside of 2.5 percent.

Mr. PORTER. We might be able to do something about it.

INCREASE IN RPG POOL

Mr. MILLER. I agree in principle, but I just get concerned. I don't know if I have time to ask any more questions or not. Are any of these other line items what you'd call real set-asides that go less than the peer review competitive that may be better to be shifted up into that \$700 million category?

Dr. PAUL. Perhaps I can answer in a slightly different way, because this idea, I think, which you are concerned about, and which I, too, am concerned about is the need to increase the pool of resources available in the grant category. It's a view that I have had since I have been in this position. It is a view that's strengthened and strongly emphasized by the Levine Report.

I think if you look at our 1995, 1996, 1997 numbers, you will see that, although over this period of time we haven't had very much of an increase in the total amount of resources—although I know the committee has worked very hard for us—but you will see the increase in the grant category has been very substantial, rising from roughly 1,800 grants, or I should say 1,808 in 1995; 1,923 in 1996; to an estimated 2,129 in 1997.

We are very anxious to increase this category. We believe it is where the greatest creativity lies, where the greatest opportunity for the "breakthroughs" we talked about earlier may come from.

While we cannot stifle important programs that are directed, to the extent we can do so, we would very much like to increase this category of funding.

RESEARCH CENTERS

Mr. MILLER. So, like the research centers, those 42 grants under other research and 176 grants, those are basically targeted?

Dr. PAUL. Well, that represents the total research centers program—

Mr. MILLER. Why do we need all those targeted ones?

Dr. PAUL. The centers are of two general types, and the purpose of centers also should be considered. There are a groups of centers funded through the National Institute of Allergy and Infectious Diseases which are called the Centers for AIDS Research, or CFARs. Their purposes are to recognize that there is value in

bringing together and creating a critical mass of scientists. Grants will pay for certain classes of costs very effectively, but there are often core facilities that are needed which would very much enhance the value of this research, which can be provided through a center mechanism.

Now, it is key that such centers be associated with institutions which have a strong record of RO1 grants; that is, we know with certainty that the investigators in those centers are meeting our highest standards of excellence.

The goal here is to provide them certain kinds of core support that they could not easily obtain through their normal grant mechanisms.

So there is a purpose here. Again, it has to be titrated. Within its realm it's a very wise investment, but the key would be that it has to form an appropriate balance with our grant portfolio.

Mr. MILLER. At some later time I'll get a better understanding of this.

SBIR JURISDICTION

Mr. PORTER. Mr. Miller, at the time Dr. Varmus first testified about NIH overall, we discussed SBIRs, just to inform you on that, and the subcommittee would have jurisdiction to do a limitation of funds, and that would not be subject to a point of order.

On the other hand, we had that jurisdiction last year and deferred to the authorizing committee that did not agree with that, but we do have the authority to do it.

Ms. Pelosi?

ROLE OF THE OAR

Ms. PELOSI. Thank you very much, Mr. Chairman.

I want to join my colleague, Congresswoman Lowey, in commending Dr. Varmus and Dr. Paul and others at the NIH for having an independent review of the AIDS research program, and for the important product that the Levine Commission produced. Everybody knows how proud we are of Dr. Varmus, those of us from the Bay area and beyond and of the many talented people he leads and some of whom he has attracted to the NIH.

I'm specifically aware, Dr. Paul, that you are a world-renowned immunologist, and that in your own research you've made a number of important discoveries in understanding the immune system. In that light, I'm so pleased that you're in the job that you have now.

Can you explain how the Office of AIDS Research, which is an issue I'm very interested in—your office—functions as an "institute-without-walls", and, in explaining it, compare to the OAR the old coordinating office approach that we had.

Dr. PAUL. Well, the purpose we have, Congresswoman Pelosi, is to plan for the utilization of the resources the Congress gives us, to work with the institutes to implement the utilization of those resources and then to evaluate them.

AIDS research is supported by every one of the institutes, centers, and divisions at NIH. That occurred because we were facing a public health emergency and it was deemed appropriate that

each of the categorical institutes should invest some of its resources in AIDS research.

Inevitably, that led us to a situation in which no one institute could deal with changing needs, because they could only have sway over the resources that had been appropriated to them.

Previously, before the OAR achieved its new responsibilities, the office had the principal responsibility to coordinate research among the institutes, but it lacked its critical planning functions, it lacked the consolidated appropriation, and it lacked its evaluation functions so that it functioned much more as an agent to be certain that the institutes worked smoothly together, rather than allowing them to move in new directions as the epidemic progressed.

LEVINE EVALUATION REPORT

Ms. PELOSI. I appreciate that. I mentioned the Levine Report earlier. Could you explain the significance of the report?

Dr. PAUL. Yes. We believe the report has significance in two principal regards. It lays out a new set of areas where it regards the greatest opportunities lie, and they are a greater emphasis on various aspects of prevention, a greater investment in fundamental research, and a reinvigorated clinical research program.

Ms. PELOSI. And support for the OAR?

Dr. PAUL. Well, it also made certain structural recommendations, and among those are heavy use of RO1 grants, a need for the development of specific criteria to classify AIDS research and non-AIDS research, and it did offer strong support for the Office of AIDS Research.

I prefer, since I am the recipient of that recommendation, not to make a big deal of that, although I agree heartily with that recommendation.

CONSOLIDATED BUDGET FOR AIDS RESEARCH

Ms. PELOSI. In what ways is the consolidated budget important to the implementation of the Levine Report?

Dr. PAUL. I personally believe it is very important. We received the Levine Report in its final version on, I believe, March 13th. The report contains within it many important recommendations. The report was finished long after our budget for fiscal year 1997 was submitted to the Department.

It is clear that if we're going to make changes in the overall goals of the NIH AIDS research program to meet the recommendations in the Levine Report and to meet the implementation plan which is now being developed, we need the flexibility to make certain changes in the way resources may be distributed. Without a consolidated appropriation, that would be exceedingly difficult to do in this period of time.

PROSPECTS FOR AN AIDS VACCINE

Ms. PELOSI. I mentioned in my opening comment that you were a renowned immunologist, and I wonder, in your expert opinion, what you think the prospects are for an effective preventive AIDS vaccine?

Dr. PAUL. I, again, am very optimistic that if we can apply the growing knowledge that we have achieved from the study of the immune system and our increasingly sophisticated virology, that there is a real prospect of developing such a vaccine.

Now, some of my colleagues may say that I'm being too optimistic, but I personally believe that, with the recognition of the role of new classes of adjuvants, with the recognition that we can use cytokines in a way to manipulate the immune response, and with the advent of the use of DNA vaccines, opportunities lie ahead of us that we really have not yet appropriately tapped. I believe that these opportunities will form the scientific basis for the development of a vaccine.

I'm not willing, as I said to Mr. Stokes, to be pinned down as to when. I think that would be foolhardy in the extreme. But I believe that the current scientific knowledge available to us and the investments we will make surely should lead us to the development of a vaccine.

Ms. PELOSI. Well, I'm sorry if I'm covering ground that Mr. Stokes already covered. Forgive me. But I do want to say in closing, Dr. Fauci this morning talked about the NIAID and its work in research for a vaccine, and that will be going down a new path, which is product development, in terms of a vaccine at the NIH.

Dr. PAUL. That is correct, but it should be recognized that the NIH's vaccine effort must have a very strong base of fundamental research now, because, as I said, it is, in fact, that which is going to fuel our ability to get products which we believe will be truly effective.

Ms. PELOSI. Thank you very much, Dr. Paul, for your testimony and for your excellent work.

Dr. PAUL. You're very welcome. Thank you.

Ms. PELOSI. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

CONSOLIDATED APPROPRIATION FOR AIDS RESEARCH

Dr. Paul, your funding has been placed into a single, consolidated account for all AIDS research for distribution to the institutes and centers of the NIH; am I correct?

Dr. PAUL. In the President's budget for fiscal year 1997 that is the request, sir.

Mr. STOKES. Has it been that way before?

Dr. PAUL. In fiscal year 1995 the monies were appropriated in the form of a consolidated appropriation. In fiscal year 1996 the continuing resolution that pertains has distributed the monies directly to the individual institutes.

Mr. STOKES. OK. What I'd like to try and find out from you is: how has life been for the Office under the consolidated AIDS account, as opposed to the non-consolidated mechanism?

Dr. PAUL. Well, in fiscal year 1995 I can give you an example of the way I believe that the availability of the consolidated appropriation was quite valuable.

In that year the President's request for NIH AIDS research was a 6 percent increase. The Congress was only able to provide a 3 percent increase.

Without the consolidated appropriation, what would have been achieved in 1995 would have been a formulaic reduction of each of the institute's requests by a comparable amount.

We in the Office of AIDS Research felt that if we were going to have an increase that was fundamentally different from the one under which the budget had been submitted, it didn't make a great deal of sense simply to use an adding machine to determine the difference. We believed that we ought to consider the scientific objectives we needed to achieve and then ask the conferees if they would be willing to entertain an alternative distribution of the resources based on those scientific needs, which they did, and which we believe allowed us to do some valuable work in that year.

Now, you must understand I became director somewhat after the time that budget had been developed, but I was director at the time that the appropriation was at that stage.

In fiscal year 1996 we've not had that authority. That certainly limits our flexibility to make changes as the science develops and as the needs of the work develop in this area.

SUPPORT FROM THE SCIENTIFIC COMMUNITY

Mr. STOKES. What has been the response, or the reaction of the extramural community and other special interests to this consolidation?

Dr. PAUL. Well our reading of it from the colleagues we consult—many of whom have participated in the development of the OAR's plan and in the work on the evaluation—is that it provides an opportunity to give leadership to this field. We believe that, on the whole, the scientific community has been very receptive to this approach.

AIDS RESEARCH LOAN REPAYMENT PROGRAM

Mr. STOKES. In your justification, I see where in fiscal year 1995 NIH awarded \$618,000 to 24 individuals under its AIDS research loan repayment program. Awards are made to 22 health professionals representing 15 recipients who entered into one-year renewal contracts, and 7 researchers who entered into initial two-year contracts. Are you familiar with those who were the recipients?

Dr. PAUL. I'm sorry. I don't know the individuals. I'm very familiar with the program, and I have sat in on some of the sessions in which credentials were reviewed. But I can't tell you precisely all of the people who have been given such awards.

Mr. STOKES. The reason I ask, Dr. Paul, is that one of my concerns is whether we are involving minorities in this area. In light of the discussion that we're having relative to the high concentration of AIDS in the minority community.

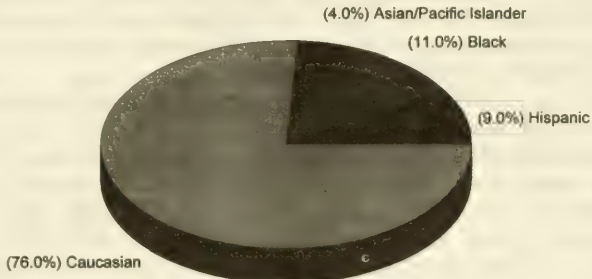
Dr. PAUL. I will certainly be able to give you that information, sir. Unfortunately, I don't have that with me at this moment.

Mr. STOKES. All right. Why don't you do this, for the record include who the recipients were, reference the ethnicity of the individuals, and highlight the current situation.

Dr. PAUL. We will certainly provide that information for you, sir.
[The information follows:]

AIDS-LRP Participants by Race

(CUMULATIVE: FISCAL YEARS 1990-1995)



Total Number of Participants=85
Number of Caucasians/Minorities=65/20

Mr. STOKES. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

LEVINE REPORT RECOMMENDATIONS ON PEER REVIEW

Dr. Paul, the Levine panel indicated that it felt the peer review process for AIDS grants had some shortcomings, and that the process didn't always identify the most promising research. Do you think this criticism is justified? And do you have any ideas about how to address the problem, if it exists?

Dr. PAUL. Yes. Well, the group, many of whom participate in the funding process, reached that opinion.

I'm not as certain from my own personal experience, but I do believe that there is a moment to re-evaluate one aspect of our peer review program for AIDS. There are series of study sections or initial review groups at NIH which explicitly deal with AIDS research applications. There are some seven conventional ones, and the former ADAMHA institutes—the National Institute of Mental Health, the National Institute of Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism—they also have a series of such study sections, which will be brought within the overall umbrella of the Division of Research Grants.

What we believe would be very valuable would be to reexamine the focus of each of these groups, because they were set up many years ago at a time when the goals of AIDS research may have been different.

While we believe that the principle of the independent review by individuals from outside should not be tampered with at all, we do think it might be valuable to be certain that the makeup or the goals of the individual groups or the kinds of grants they review should be scrutinized to be certain that that's been done appropriately, and I believe that was the principal concern on the part of the members of the working group that wrote that recommendation.

Mr. PORTER. The Levine panel recommended making the consideration of priorities in AIDS research part of the peer review process. Wouldn't that be a new role for the study sections, which are supposed to review for technical merit but leave the priority-setting to the institute's advisory councils?

Dr. PAUL. You're quite right, sir. In our initial discussions at NIH, in the process of preparing our implementation plan, this is the very first issue which we have discussed. I think there was universal agreement on the part of the NIH directors, Dr. Varmus and myself, that that was probably one area where we felt the panel might not have given adequate consideration, because we do believe that it is quite essential that the peer review process be removed from a planning process. The purpose of peer review is to make a scientific judgment as to whether or not a grant is meritorious in its own right.

The purpose of secondary review is to look to the whole issue of whether it meets the goals of the program. I think that this distinction is a very wise one.

Perhaps Dr. Varmus would like to comment on this, an area I know he's deeply concerned about.

Dr. VARMUS. This is not to say that the significance of the research is not an issue in the initial peer review process—that is, the scientific impact of any research proposal, of course, is taken into consideration. But to ask the peer reviewers to try to align their evaluation of a series of grants with their assumptions of what might be specific targeted priorities of various institutes in the Office of AIDS Research, to my mind, would be a mistake.

I might also add, Mr. Porter, that in this era of very difficult funding, with success rates quite low in many categories, it's not surprising that any group that evaluates a program will have some concerns about peer review. It is an imperfect system.

As you've heard previously, there are many initiatives underway to try to improve the system. In fact, we've made some gains. I'm currently in the late stages of recruiting a new director of the Division of Research Grants, and I'm hoping that when that new person is on board we'll have yet further initiatives in this area.

Mr. PORTER. Thank you, Dr. Varmus.

MECHANISMS TO IMPLEMENT LEVINE REPORT

Do you expect, Dr. Paul, to use either the transfer authority you will receive in the omnibus appropriations bill or the director's 1 percent transfer authority in the current fiscal year to realign AIDS research among institutes to conform to the Levine panel recommendations?

Dr. PAUL. For fiscal year 1996, Mr. Porter, I assume you're referring to?

Mr. PORTER. Yes.

Dr. PAUL. I think in fiscal year 1996 we'll do our utmost to try to respond to the Levine panel by the use of our discretionary fund. We believe that will have the greatest impact with the least disruption on the institutes.

We are somewhat concerned about making substantial changes in distributions this late into the fiscal year because we do believe it provides a difficulty for the institutes and their planning.

Nonetheless, we believe the consolidated appropriation is a valuable tool. Of course, whatever the Congress decides on for 1996, we will gratefully accept. Having a consolidated appropriation for 1996, of course, would have an importance in terms of its acting in a way to raise the likelihood we would receive that for 1997.

CHANGES IN FY 1997 ALLOCATION

Mr. PORTER. Do you expect to recommend changes to the allocation of AIDS funds among institutes in your fiscal year 1997 budget request based on the Levine panel report?

Dr. PAUL. Yes. I believe we will make some changes. They obviously will need to wait upon our development of an implementation plan, but once that plan has been developed we will review the proposed budget allocations, and if there is need in order to accomplish the goals or the implementation of the report, we will certainly wish to make certain changes.

Mr. PORTER. Ms. Pelosi?

PRECEDENT OF FY 1996 ACTION REGARDING CONSOLIDATED
APPROPRIATION

Ms. PELOSI. I just want to follow up on one question that you had, Mr. Chairman. I listened very carefully to what you said about the impact of the 1997 approach without the consolidated AIDS budget for the Office of AIDS Research. Could you state for the record that it would be important that the 1996, should it stay the way it is, not be considered a precedent for 1997, and point out what difference that would make.

Dr. PAUL. Well, indeed, the precedent that would be set by not having a consolidated appropriation in 1996 is one that we would certainly hope would not be sustained in 1997. We believe that the consolidated appropriation is the most flexible means available to make the changes that are needed in a manner that is least disruptive to the functions of the institutes that does not impact on the resources they receive for non-AIDS research, is most easy to carry out, and gives them the greatest forewarning of what changes will occur so one can make these changes as early as possible.

Transfer authorities, since they operate late, after the appropriation I think place a greater burden on the institutes of uncertainty in their funding.

And there is no doubt: the greater the certainty they have, the more effective they will be with the resources they receive.

Ms. PELOSI. Thank you, Dr. Paul.

Dr. Varmus?

Dr. VARMUS. I just wanted to draw your attention, in response to your concern, and Mr. Porter's as well, about the use of the 1 percent transfer authority to the fact that I have used it this year to transfer money for financing of the ACTG—AIDS clinical trials groups—to NIAID in support of the AIDS program, and I am perfectly prepared to use the 1 percent transfer authority, in consultation with Dr. Paul, when I think that it's appropriate to do so to advance the cause of AIDS research.

Ms. PELOSI. I appreciate that, Dr. Varmus. Thank you.

A concern that I have, obviously, is that the OAR is authorized to function with the consolidated budget. We departed from that for 1996. We're down the path half a year. If we are to stay on that particular course for 1996, there are some of us who don't want that to be considered a precedent.

The further concern that we have is that, looking at the performance for 1996, I don't know what's going to happen for the budget for 1997, and I think it would be unfortunate if we had to put off the functioning under the authorization until 1998.

Dr. VARMUS. The Administration agrees with you and we've come forward with a consolidated budget.

I should also point out that, of course, the budget distributed for 1996 was in accord with the original plan of the OAR.

Ms. PELOSI. Thank you very much, Dr. Paul, Dr. Varmus, and others.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Istook?

Mr. ISTOOK. Thank you, Mr. Chairman.

NON-COMPETING RESEARCH

Dr. Paul, I wanted to ask you something, and Mr. Miller touched somewhat on this, and this will be a question for you, too, Dr. Varmus.

Of course, in the mechanism breakdown you don't specify as which grants are non-competing and which are competing, and, as you alluded to before, Dr. Paul, certainly you cannot expect research projects to arbitrarily confine themselves to a 12-month period. Even though you may need to renew grants or projects, the research, itself, may need—I notice basically throughout the different institutes there is probably usually a three-to-one or four-to-one ratio of non-competing to competing.

But what I wanted to ask you about, though, was if you have any sort of breakdown of what you might call an aging of accounts. For example, of the non-competing grants, which one of those basically reflect grants that have been non-competing for three years or non-competing for eight years, or whatever the applicable time frames may be?

I'm interested to understand that process, and also to know if there is—there may be, but I just don't know—when you talk about the peer review, is there a different process for evaluating the continuation of the non-competing grants than there is of the award of the competing ones?

Dr. VARMUS. Would you like a generic answer for NIH?

Mr. ISTOOK. If that would be helpful, yes. If there's anything distinctive about—

Dr. VARMUS. I think it might be easier. Mr. Istook, the average length of an award at NIH in the RPG pool—research project grant pool—is just under four years. That is a number to which we're very sensitive. In fact, this committee, in 1991, I believe, was concerned about the increasing average length of awards. It had crept up to 4.3 years, and that increased our commitment base to a level at which very small perturbations in our annual increase caused a tremendous decline in success rates—in fact, ignited a crisis in biomedical research. So we are sensitive to lowering that.

Mr. ISTOOK. Sure. By the way, when you mentioned that 4.3 ratio, is that saying average—

Dr. VARMUS. It's not a ratio.

Mr. ISTOOK. [continuing]. Duration of grants, or when you adjusted for the fact the average duration of dollars as opposed to number of grants, since they vary in balance?

Dr. VARMUS. That was the average length of a grant in the RPG pool.

Mr. ISTOOK. Okay.

Dr. VARMUS. With respect to review, the non-competing awards are given an administrative review only. That is, they are looked at with respect to budget by program officers in the institutes. They are not subjected to peer review by initial review groups in the Division of Research Grants, whereas the new and competing renewals are subjected to peer review for technical and scientific excellence.

Mr. ISTOOK. When it comes to the add-on costs, the indirect overhead or administrative overhead, is there any different process or

criteria that are applied when a non-competing grant is coming up for renewal but there's an adjustment of those factors once they've got a grant?

Dr. VARMUS. In general, the non-competing awards receive indirect cost rate that was determined at the time of the award.

Mr. ISTOOK. And not adjusted thereafter?

Dr. VARMUS. That has generally been true.

Mr. ISTOOK. Okay.

Dr. VARMUS. And, of course, those rates are determined by negotiation between the Government and the institution.

Mr. ISTOOK. Is that the same on administrative overhead as it is for the indirect?

Dr. VARMUS. The indirect cost has traditionally been what we now refer to as "administrative cost" and "facilities cost."

Mr. ISTOOK. Yes.

Dr. VARMUS. You'll recall that administrative costs have been capped at 26 percent. On average they're about 24.8 percent nationwide. And the facilities costs are determined by negotiation, but they are much more variable, as I think we discussed last Thursday.

Mr. ISTOOK. Right. I would be interested—I'm using the term "aging accounts." You may have some other term you use, of course, for it. But I would be interested to see that breakdown over the last five years, how that process has been, especially when you look at it not just on the—you can say, "Well, five out of ten grants have been that way," but that may not reflect five out of ten grant dollars.

Dr. VARMUS. Yes. That's correct.

Mr. ISTOOK. So I would appreciate that it be done in a manner that reflects the grant dollars, not just the numerical count of the grants, themselves.

Dr. VARMUS. With respect to what now?

Mr. ISTOOK. To how many of them in the non-competing area each year are a grant that's been a two-year grant, three-year, six, whatever it may be on that, to look at that over the last five years. In fiscal year 1992, these were the ratios involved, in fiscal year 1993, in fiscal year 1994, and so forth, to look at the history of that.

Am I making sense?

Dr. VARMUS. I'm not sure I know exactly what you mean. Maybe we can do that for the record.

Mr. ISTOOK. Yes. We can do that for the record.

Dr. VARMUS. We'd like to know exactly what you have in mind so that when we do this work we supply you the numbers you desire.

[The information follows:]

NON-COMPETING RESEARCH PROJECT GRANTS

There were 17,318 non-competing research project grants funded during FY1995. Two thirds of these awards had competed within two years of their current award. This has risen only slightly over the past five years. The following table shows the trend from FY 1991 to FY 1995 for the number of grants as well as for the dollars involved.

NIH Noncompeting Continuation Research Project Grants
percent competed within two years of their award

Year	Number	Amount	Percent of Total	
			Number	Dollars
91	17,108	\$3,682,743	61.9	58.8
92	17,524	\$3,923,610	62.7	61.0
93	18,106	\$4,305,846	65.1	64.3
94	17,842	\$4,410,958	63.6	62.2
95	17,318	\$4,449,791	65.9	62.4

Another way to look at the length of time they had been active research projects is to look at their overall period of support. Among them, 59 percent of the awards were in the first 1-5 years of support, 20 percent were in their 6-10 year of support, and less than two percent had already received support for at least 25 years. In terms of dollars expended for non-competing awards, about half of the dollars were expended for the projects in their first segment of support (that is, 1-5 years); 22 percent went to projects in years 6-10 of support and a little over two percent went to projects that had had long term support, that is, 25 years or more. This has not changed appreciably over the past several years, as the following table shows. The NIH extramural program depends on the ongoing competition among scientists to ensure that we are funding the best science.

NUMBER OF NIH NONCOMPETING CONTINUATION
RESEARCH PROJECT GRANTS
FY 1991-1995

AGE OF AWARD AS SHOWN BY SUFFIX YEAR

FY	TOTAL	1-5	6-10	11-15	16-20	21-25	26-30	31+
1991	17,108	9,585	4,434	1,715	756	335	182	101
%	100%	56.03%	25.92%	10.02%	4.42%	1.96%	1.06%	0.59%
1992	17,524	9,892	4,380	1,816	803	345	177	111
%	100%	56.45%	24.99%	10.36%	4.58%	1.97%	1.01%	0.63%
1993	18,106	10,259	4,317	1,961	905	362	184	118
%	100%	56.66%	23.84%	10.83%	5.00%	2.00%	1.02%	0.65%
1994	17,842	9,894	4,082	2,144	974	417	204	127
%	100%	55.45%	22.88%	12.02%	5.46%	2.34%	1.14%	0.71%
1995	17,318	10,140	3,462	2,049	930	431	171	135
%	100%	58.55%	19.99%	11.83%	5.37%	2.49%	0.99%	0.78%

AMOUNT OF NONCOMPETING CONTINUATION
RESEARCH PROJECT GRANTS

FY	TOTAL	1-5	6-10	11-15	16-20	21-25	26-30	31+
1991	\$3,682,743	\$1,837,144	\$1,007,241	\$437,396	\$228,400	\$85,465	\$58,736	\$28,361
%	100%	49.89%	27.35%	11.88%	6.20%	2.32%	1.59%	0.77%
1992	3,923,610	1,965,948	1,054,701	462,969	241,889	99,804	58,353	39,946
%	100%	50.11%	26.88%	11.80%	6.16%	2.54%	1.49%	1.02%
1993	4,305,846	2,140,560	1,135,051	528,381	293,186	108,369	56,767	43,532
%	100%	49.71%	26.36%	12.27%	6.81%	2.52%	1.32%	1.01%
1994	4,410,958	2,156,599	1,127,993	565,969	318,517	128,637	64,057	49,186
%	100%	48.89%	25.57%	12.83%	7.22%	2.92%	1.45%	1.12%
1995	4,449,791	2,298,478	1,002,271	585,875	305,237	149,378	54,652	53,900
%	100%	51.65%	22.52%	13.17%	6.86%	3.36%	1.23%	1.21%

Mr. PORTER. Thank you, Mr. Istook.

Dr. Paul, we have other questions for the record for you, which we ask that you respond to promptly, if you will.

Mr. PORTER. We thank you for the wonderful job that you're doing at OAR and for humankind, generally, and for your excellent testimony today.

Dr. PAUL. Thank you, Mr. Porter.

Mr. PORTER. The subcommittee stands in recess until 10:00 a.m. tomorrow.

[The following questions were submitted to be answered for the record:]

IMPLEMENTATION OF THE LEVINE REPORT RECOMMENDATIONS

Mr. Porter: Has NIH developed a strategy for reviewing the Levine Panel's recommendations, reporting its conclusions, and implementing the necessary changes?

Dr. Paul: Yes, we have initiated a series of meetings to prepare our response to the recommendations through an implementation plan. Dr. Varmus and I are meeting with the Institute Directors to address each of the 14 major recommendations of the Levine Report. We are also developing strategies to address the recommendations of the individual panel reports.

Mr. Porter: You have indicated that you plan to use your discretionary fund to help implement the Levine panel recommendations. Can you give us an idea of how much of the fund you plan to spend and for which purposes?

Dr. Paul: The first priority of the Levine report is to increase the number of unsolicited investigator-initiated grants. It is therefore my intention to use the majority of the \$10 million discretionary fund to increase the research project grant pool. The OAR has asked the institutes to submit to us proposals for funding additional grants.

DEFINITION OF AIDS RESEARCH

Mr. Porter: One of the Levine panel's criticisms is that some NIH Institutes defined their AIDS portfolios rather loosely or imprecisely. But doesn't that go against NIH's contention that much of AIDS research has broader applicability to other diseases and molecular processes?

Dr. Paul: No, these two issues are not in conflict. In the effort to quickly respond to the public health crisis, a broad spectrum of basic research was supported and considered relevant to HIV. At that time little was known about the disease, and it was impossible to know where we might find answers to these complex questions. In the intervening years, we have amassed a greater understanding of HIV and its sequelae. Therefore, it is now possible to reevaluate our previous scope of investigation to make more effective use AIDS funding, which still includes a broad base of basic research.

SINGLE CONSOLIDATED APPROPRIATION FOR AIDS RESEARCH

Mr. Porter: Now I'd like to switch to a subject which has been contentious for all of us--your budget request for a single, consolidated AIDS appropriation which would go directly to your office for transfer to the individual Institutes. I think it would be helpful to put a few facts into the record first:

It is correct, is it not, that you have never had the authority envisioned in the authorizing statute—of receiving one lump sum for AIDS with unfettered authority to transfer it to the individual Institutes as you like. In 1995, you received a consolidated appropriation, but the amount each Institute would receive for AIDS was identified in the conference report, so that you had no flexibility to change these allocations without a reprogramming from Congress. In 1996, all funding was allocated to the individual Institutes. No specific earmarks were identified for AIDS so that your office could determine how much each Institute would spend on AIDS. If you need to transfer funds from one Institute to another for AIDS activity, you can do it with the special transfer authority provided in the omnibus appropriations bill. Am I stating the facts correctly for the record?

Dr. Paul: The Administration continues to support a consolidated appropriation for NIH AIDS research. It is correct that in FY 1995, the OAR received a consolidated appropriation. Prior to the conference, we requested the opportunity to include a revised distribution in the conference report in order to expedite the desired changes in the distribution. It was our understanding, based on the NIH Revitalization Act of 1993, that we had the authority to change the distribution up to thirty days after the appropriation without a reprogramming request. In FY 1996, the House report language stated that the total amounts for AIDS should be determined not by the OAR, but by the Director of NIH. It is correct that the transfer authority provided in the recent omnibus appropriations bill would allow us to transfer funds from one Institute to another for AIDS activities.

TRANSFER OF FUNDS

Mr. Porter: In fact, since the authorizing legislation would require you to transfer all AIDS money back to the individual Institutes within 30 days of enactment of the appropriations bill, the transfer authority you received in 1996 actually provides you with additional powers throughout the fiscal year beyond what you would have under the authorizing statute. Is that correct?

Dr. Paul: I do not believe that is correct. It is my understanding that the transfer authority included in the FY 1996 omnibus bill requires that these transfers occur within 30 days of enactment. It does not provide transfer authority throughout the year. Thus, we do not believe that we have been provided additional powers.

ALLOCATION OF AIDS FUNDS

Mr. Porter: If the committee were to repeat in 1997 its 1996 practice of not earmarking a separate appropriation for AIDS, but if we consulted with you at the time of conference about your most up-to-date allocation of funds for each Institute and incorporated that into the conference agreement, wouldn't that produce the same result as if we had provided a separate AIDS appropriation for you to distribute?

Dr. Paul: Such a consultation at the time of conference would not necessarily produce the same result as a separate AIDS appropriation. A complex series of steps also would be required to achieve this purpose. It is particularly unclear whether such a consultation could produce the desired result without explicitly defining AIDS and non-AIDS dollars. Report language and changes in the apportionment documents might also be required.

SPENDING IN ACCORDANCE WITH THE COMPREHENSIVE PLAN

Mr. Porter: Regardless of the structure of the appropriation, doesn't the apportionment for each Institute from OMB require the Institute to spend its AIDS funding consistent with the purposes identified in your AIDS plan?

Dr. Paul: In the past, the apportionment document has not required the Institutes to spend AIDS resources in accordance with the plan. In FY 1996, the apportionment documents include a footnote stating, "The amounts for AIDS research identified in this document reflect the distribution of AIDS resources and approved activities under the FY 1996 NIH Plan for HIV-Related Research, both of which were determined by the Director, Office of AIDS Research in accordance with the requirements of Sec. 2353 of the Public Health Service Act. Any change in these amounts for AIDS research and activities must be submitted to OMB after approval by the Director of the Office of AIDS Research."

Mr. Porter: Have you ever had a problem with an institute resisting or refusing to comply with the AIDS strategic plan? What mechanisms are in place to resolve such a problem should it occur?

Dr. Paul: As the Levine report pointed out, there have been instances where some Institutes have taken a very liberal interpretation of the relationship between some AIDS research and the objectives of the plan. No specific mechanism exists to resolve differences in judgment regarding compliance with the plan. However in such cases, I would anticipate that the Director of OAR and the Director of the Institute would work together to reach agreement. For example, I have met on a number of occasions with the Director of NCI to resolve our mutual concerns about decisions that were made previously. The only other mechanism lies in reassessing the institute's budget in future years.

PERCENTAGE OF TRANSFER AUTHORITY

Mr. Porter: If we again provide transfer authority for you in the 1997 bill, what percentage transfer authority would you suggest?

Dr. Paul: Again, we support a single appropriation. As to your question, while we have yet to have experience with the current 3 percent transfer authority, it would appear to me to be sufficient. However, it is important that such authority

provides the ability to transfer funds into an institute without a restriction regarding the degree to which its budget may be enhanced.

SHIFT FROM INTRAMURAL RESEARCH

Mr. Porter: From 1995 to 1997, there is a substantial shift in the overall NIH AIDS budget from intramural research to extramural research project grants. Which Institutes are most affected by this change?

Dr. Paul: The shift is primarily due to a reduction by the NCI in its intramural program, in keeping with the recommendations of several advisory groups to the NIH.

DIRECT OPERATIONS OF THE OFFICE OF AIDS RESEARCH

Mr. Porter: Identify the FY95-97 budget for the direct operations of your Office, separately identifying the size of the discretionary fund in each of those years.

Dr. Paul: The table below provides the information:

Office of AIDS Research			
Office of the Director			
(Dollars in thousands)			
	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
OAR Operating Budget	\$7,601	\$8,481	\$7,205
Administrative Support Outside of OAR	959	972	972
Intramural AIDS Targeted Antiviral Program	6,648	6,450	5,450
AIDS Loan Repayment	618	695	973
Emergency Discretionary Fund	8,568	10,000	10,000
TOTAL	24,394	26,598	24,600

NUMBER OF RESEARCHERS

Mr. Stokes: What is the Office of AIDS Research doing to increase the number of African American and other minority research investigators involved in AIDS research?

Dr. Paul: NIH focuses attention on the recruitment of minority physicians, particularly African Americans, to conduct research and administer research programs at the NIH. The OAR provides funding and support for the NIH AIDS Loan Repayment Program, which was authorized by Congress to encourage qualified physicians and scientists to engage in AIDS-related research at the NIH. The program strives to attract qualified minority researchers. The Loan Repayment Program Regarding Clinical Researchers from Disadvantaged Backgrounds, also authorized by Congress, has been established by NIH, based on the AIDS Loan Repayment model. This program provides loan repayment for qualified health professionals from disadvantaged backgrounds to conduct clinical research as employees of the NIH. The OAR has provided support for a series of meetings since 1989 sponsored by the Public Health Service, including the National Congress on the State of HIV/AIDS in Racial and Ethnic Communities.

The OAR supported the AIDS Postdoctoral Fellows Meeting that provided minority predoctoral and postdoctoral fellows, junior faculty, and physicians in training the opportunity to interact with senior AIDS researchers. State-of-the-art information on AIDS research was discussed. The meeting served to enhance recruitment of minorities into the NIH and NIH-sponsored Institutional Training Grant programs.

Mr. Stokes: What efforts has the office undertaken to educate minorities on opportunities that are available in biomedical research?

Dr. Paul: OAR supports activities aimed at informing minority biomedical and behavioral health professionals about opportunities in the AIDS Loan Repayment Program and NIH research through sponsorship of exhibits and attendance at meetings such as the National Medical Association, the Student National Medical Association, the American Medical Student Association, and through outreach to the Dean of Students and Financial Aid Officers at Historically Black Colleges and Universities.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant AIDS clinical trials across the institutes and centers?

Dr. Paul: The NIH clinical trials effort includes numerous clinical trials networks, sponsored by NIAID, NICHD, NEI and NIH intramural sites. More than 45,000 patients have been enrolled to date in NIH-sponsored trials, which have involved the evaluation of nearly 80 agents. There are currently 70 clinical trials enrolling patients studying 78 different therapeutic agents. Accomplishments in NIH-sponsored clinical trials include demonstration of the efficacy and clinical benefits of AZT for both adults and children with early and asymptomatic infection; the safety and efficacy of ddI and ddC for adults and children; the antiviral activity of interferon

and its benefits for reducing Kaposi's sarcoma lesions; the utility of paclitaxel in advanced Kaposi's sarcoma; the benefits of nimodipine for the treatment of AIDS dementia complex; and the therapeutic benefits of ddC plus AZT combination therapy. A trial sponsored by NIAID and NICHD demonstrated that AZT administered during gestation and labor and to the infant after birth reduces the rate of HIV transmission by approximately 67 percent.

Accomplishments of NIH-sponsored trials in the past year include the completion of two combination nucleoside trials in the adult and one in the pediatric HIV-infected populations which demonstrated clinical superiority of ddI monotherapy and ddI/AZT combination therapy over AZT monotherapy. Other trials have shown the clinical benefit of treatment with Thalidomide for oral aphthous ulcers; recombinant human growth hormone for treatment of AIDS-associated wasting syndrome; and megestrol acetate for wasting syndrome. Additional NIH trials have contributed to the further understanding of the use of protease inhibitors, nucleoside analogs, and nonnucleoside reverse transcriptase inhibitors, and the impact of these agents on viral load and on clinical outcomes.

NIH research on therapies for opportunistic infections have greatly contributed to extending and improving the quality of life for HIV-infected individuals. Accomplishments include demonstration of the efficacy of TMP-SMX, atovaquone, dapsone, and aerosolized pentamidine for the prevention of *Pneumocystis carinii* pneumonia, fluconazole for the treatment of cryptococcal meningitis and prevention of fungal infections; foscarnet for the treatment of CMV retinitis; IV gamma globulin for reducing OIs in HIV-infected children; the combination of pyrimethamine and clindamycin for toxoplasmic encephalitis; and itraconazole for disseminated histoplasmosis.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for AIDS clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Paul: The FY 1997 budget request includes \$372,790,000 for adult and pediatric clinical trials. In FY 1996 the total is an estimated \$374,915,000. The total for FY 1995 was \$366,522,000; and for FY 1994 was \$358,810,000.

Mr. Stokes: What is the office doing to ensure the appropriate enrollment of African Americans and other minorities, and women in AIDS clinical trials?

Dr. Paul: The OAR is committed to assuring that the participation of specific populations in NIH-funded clinical trials reflects the changing demographics of HIV infection and AIDS, including women, children, adolescents, drug users, minorities, the urban poor, and individuals residing in rural areas. Recruitment and enrollment of these underrepresented populations is a high priority in NIH-sponsored studies, and these issues are specifically addressed in the NIH Plan for HIV-Related Research developed by the OAR. NIH has published and implemented strengthened guidelines for the inclusion of women and minorities in clinical studies, and the Office of Research on Women's Health and the Office of Research on Minority Health continue to monitor compliance with these guidelines.

In addition, the AIDS Clinical Trials Group (ACTG) of the NIAID supports the AIDS Clinical Trials Infrastructures in Minority Institutions to enhance HIV clinical research performed at minority institutions. Four institutions, located at Howard University, Meharry Medical College, the University of Puerto Rico, and the University of Hawaii received 4-year awards as adult ACTUs. This program increases the number of minority staff involved in ACTG research and the number of minority participants in the studies.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: Specifically, what activities are underway to address the "Changing Faces of AIDS" and does this office work to ensure that change is addressed and reflected in the direction of AIDS research and outreach across the institutes, centers and divisions?

Dr. Paul: The central responsibilities of the OAR to plan, evaluate, and budget for all NIH AIDS research provides the mechanism to ensure that AIDS research across all of the institutes, centers, and divisions addresses the changing face of the epidemic and the changing scientific needs. An important element of both the OAR planning and evaluation processes is the inclusion of representatives of the AIDS community. In the recent evaluation of the NIH research program, representatives of 17 different AIDS community organizations, including women and minorities, contributed to the year-long process. In addition, public hearings were held to allow even greater participation of the AIDS-affected community.

Although the OAR does not directly fund research projects, the OAR has used the resources of its Emergency Discretionary Fund to support ICD research projects important to the issues of AIDS and minorities.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component of the research continuum, what are the most significant outreach and public education activities underway at the office? How much is included in the FY 97 budget for the office's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Paul: The OAR's mandate is primarily to plan, coordinate, evaluate and fund the AIDS-related activities of the NIH institutes, centers, and divisions. Therefore, most of the outreach and public education activities are carried out in the ICDs and the National Library of Medicine. To assist in the coordination of these efforts, the OAR maintains an Information Dissemination Coordinating Committee, and the annual NIH Plan and Consolidated Budget for HIV-Related Research, prepared by the OAR, includes information dissemination activities. The OAR also maintains a site on the NIH Home Page of the Internet.

The NIH as a whole provides an extensive range of programs to educate health care professionals and their patients about the results of HIV research and the opportunities to volunteer in HIV-related clinical trials. A "Guide to NIH HIV/AIDS Information Services" was

developed by NLM and OAR details these programs. For example, the AIDS Clinical Trials Information Service sponsored by NIAID is a toll-free telephone service providing free, up-to-date information on open clinical trials evaluating experimental therapies. AIDSTRIALS is an NLM online database of information concerning HIV-related clinical trials. Several ICDS produce and distribute pamphlets, factsheets, press releases, and other materials for the public and for physicians to provide to their patients. Since 1991, the NIH has used a dedicated system of electronic and print notification, collectively known as Clinical Alerts to rapidly disseminate to health care professionals, patients, the news media, and the public information that critically affects the care of patients, such as results of HIV-related clinical trials. These alerts are available online and are also provided for dissemination in academic health centers and more than 3,000 hospitals. As part of a larger program of training in the use of on-line databases that NLM has been conducting with the Historically Black Colleges and Universities, a new AIDS module has been created, with materials specifically tailored for minority health professionals. NIDA sponsors a campaign focusing on teenagers, young adults, and women called "Get High, Get Stupid, Get AIDS" warning of the relationship between drug and alcohol use and the risk of HIV infection.

The OAR sponsors and supports a series of regional meetings and workshops around the U.S. and in Puerto Rico to bring the latest research advances to physicians and clinicians who are treating HIV-infected individuals. An important challenge to the NIH is to provide accurate and timely treatment information to people in underserved communities and communities of color.

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account. Is this the case in your office, explain?

Dr. Paul: The OAR-sponsored regional meetings and workshops are primarily state-of-the-art conferences targeted to communities that do not have ready access to major medical centers and have been held predominantly in minority communities. These meetings are funded from the research management and support account.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between the AIDS Office and the Office of Research on Minority Health? Are there specific AIDS projects that are funded totally by the Office of Research on Minority Health, and if so, why and which are they? For the record provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Paul: The Office of Research on Minority Health (ORMH) works with the Office of AIDS Research through collaboration with the Institutes, Centers and Divisions. There is one specific AIDS project that is funded totally by ORMH. This project, The Minority Adolescent HIV Research Initiative, was established in 1994 by the National Cancer Institute (NCI), in collaboration with ORMH, as a demonstration project in Washington, D. C. to respond to the changing face of AIDS. The project has been funded for \$2.2 million in 1994, \$2.9 million in 1995 and \$3.4 million in 1996.

Mr. Stokes: Are there specific projects that are co-funded by the Office of AIDS Research and the Office of Research on Minority Health, explain?

Dr. Paul: In conjunction with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH), and the National Center for Research Resources, the ORMH supports collaborative proposals submitted by investigator pairs. One investigator of the pair must be from a Center for AIDS Research (CFAR) and the other investigator from a Research Center in Minority Institutions (RCMI) Program. The purpose of this project is to develop a level of expertise in minority institutions that will increase the possibility of successful competition for funding of AIDS research projects.

JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
Office of AIDS Research

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NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research
(INCLUDING TRANSFER OF FUNDS)

For carrying out Part D of Title XXIII of the Public Health Service Act, \$1,431,908,000. Provided, That the Director of the Office of AIDS Research shall transfer funds from this appropriation the amounts necessary to carry out subsection 2353 (d) of the Act.

Note: A regular appropriation for this account had not been enacted. The 1996 amounts included in this budget are based on comparable levels provided in three continuing resolutions: P.L. 104-91, P.L. 104-92, and P.L. 104-99.

Office of AIDS Research

Amounts Available for Obligation

	<u>1995 Actual</u>	<u>1996 Estimate</u>	<u>1997 Estimate</u>
Appropriation	\$1,337,606,000	—	\$1,431,908,000
Reduction in accordance with P.L. 103-333	-2,185,000	—	—
Recission in accordance with P.L. 104-19	-1,851,000	—	—
Subtotal, Adjusted appropriation	<u>1,333,570,000</u>	<u>—</u>	<u>1,431,908,000</u>
Comparative transfers from:			
National Cancer Institute	305	\$225,790,000	—
National Heart, Lung, and Blood Institute	—	57,925,000	—
National Institute of Dental Research	—	12,309,000	—
National Institute of Diabetes and Digestive and Kidney Diseases	—	11,735,000	—
National Institute of Neurological Disorders and Stroke	—	23,807,000	—
National Institute of Allergy and Infectious Diseases	—	596,018,000	—

National Institute of General Medical Sciences	---	\$26,135,000	---
National Institute of Child Health and Human Development	---	60,713,000	---
National Eye Institute	---	9,125,000	---
National Institute of Environmental Health Sciences	---	6,051,000	---
National Institute on Aging	---	1,785,000	---
National Institute of Arthritis and Musculoskeletal and Skin Diseases	---	4,039,000	---
National Institute on Deafness and Other Communication Disorders	---	1,650,000	---
National Institute of Mental Health	---	93,556,000	---
National Institute on Drug Abuse	---	153,331,000	---
National Institute of Alcohol Abuse and Alcoholism	---	10,135,000	---
National Institute of Nursing Research	---	4,896,000	---
National Center for Research Resources	---	68,370,000	---

National Center for Human Genome Research	-----	\$1,000,000	-----
John E. Fogarty Inter- national Center for Advanced Study in the Health Sciences	-----	9,694,000	-----
National Library of Medicine	-----	3,162,000	-----
Office of the Director	-----	26,598,000	-----
Office of AIDS Research Discre- tionary Fund			
Subtotal, adjusted budget authority	<u>\$1,333,875,000</u>	<u>1,407,824,000</u>	<u>\$1,431,908,000</u>
Unobligated balance, available start of year	18,413,000	18,106,000	-----
Unobligated balance, available end of year	-18,106,000	-----	-----
Unobligated balance lapsing	-497,000	-----	-----
Total, obligations	<u>1,333,385,000</u>	<u>1,425,930,000</u>	<u>1,431,908,000</u>

Justification**Office of AIDS Research**

FY 1995	FY 1996	FY 1997
<u>Actual</u>	<u>Estimate</u>	<u>Estimate</u>
\$1,333,875,000	\$1,407,824,000	\$1,431,908,000

General Statement

The FY 1997 budget request for AIDS research at NIH is \$1,431,908,000. This represents a 1.71% increase over the FY 1996 Estimate. Under the provisions of the NIH Revitalization Act of 1993, the OAR receives directly from the President and the OMB all funds available for AIDS activities of the NIH. Thus, this request reflects a single consolidated amount for all AIDS research provided to the OAR for distribution to the institutes and centers of the NIH. This consolidated appropriation allows the OAR to effectively manage the research resources on the basis of sound scientific judgment taking advantage of the most promising research opportunities.

The FY 1997 budget request, developed by the OAR, represents the resources needed at a critical juncture in research on HIV infection and AIDS. The nation's investment in AIDS research is now reaping benefits and opening new and exciting scientific avenues to pursue. These advances will contribute not only to progress in AIDS research, but to many other important research areas. This budget is based on the FY 1997 Plan for HIV-Related Research, which reflects a frank assessment of our successes and shortcomings and charts a course for the future, based on a broad consensus of the scientific community. Through this FY 1997 Plan and Budget, the OAR has refocused scientific priorities and shifted resources to meet these priorities.

Overall Budget Policy

The President's request of \$1,431,908,000 is proposed for the HIV/AIDS activities of the National Institutes of Health. Funding for the Office of AIDS Research during the last five years has been as follows:

	<u>Amount</u>
FY 1992	\$1,047,456,000
FY 1993	1,071,457,000
FY 1994	1,298,471,000
FY 1995	1,333,875,000
FY 1996	1,407,824,000

The HIV/AIDS Pandemic

In the United States today, as well as in dozens of countries worldwide, AIDS is the number one cause of death among young adults. The HIV/AIDS epidemic in the United States is shifting into new populations, disproportionately affecting women, young adults and persons from racial and ethnic minorities. The proportion of newly reported AIDS cases as a result of heterosexual transmission has dramatically increased. In 1994, for example, one in every three deaths among African-American men and one in every five deaths among African-American women between 25 and 44 years of age resulted from HIV-related illnesses. Rates of HIV transmission among gay men have decreased, but remain unacceptably high, especially among young gay men and gay men of color. In addition, the epidemic is shifting regionally, with an increasing proportion of cases reported in the Southern and Southeastern United States. The increases in infected adolescents means that these young people are acquiring a disease with a known case-fatality rate of at least 62 percent within a decade after infection, before the opportunities of adulthood have begun to be realized.

The World Health Organization (WHO) estimates that world-wide 18.5 million adults and 1.5 million children have become infected with HIV and that nearly 10,000 new infections occur each day. More than 2.5 million adults, children, and infants have died from HIV/AIDS. Approximately 90 percent of HIV-infected individuals are in developing countries of the world, with Africa and now Asia bearing the greatest burden of the epidemic.

There are some encouraging signs, such as the decreasing numbers of HIV-infected infants in the United States and other developed countries as a result of the increasing use of antiretroviral drugs in HIV-infected pregnant women. NIH-sponsored research demonstrated that use of one of these drugs, zidovudine, in pregnant women and in newborns dramatically reduces risk of HIV transmission from mother to infant. Other recent prevention successes include the finding that providing treatment for other sexually transmitted infections to persons at high-risk of acquiring HIV can reduce the risk of HIV transmission. Provision of clean needles to injection drug users also has been shown to reduce HIV transmission rates. Recent results also have shown that persons with occupational exposure to HIV infection, such as health care workers, benefit from immediate post-exposure treatment with anti-HIV drug therapy. These examples of the possibilities for curtailing the epidemic underscore the need for a sustained investment in and commitment to HIV/AIDS research.

The Benefits of AIDS Research to Other Diseases

The effort to understand HIV and AIDS has led to, and will continue to result in, scientific strides that benefit research on many other diseases. AIDS research has accelerated study of the human immune system. This basic immunologic information is being applied to research to

better understand and treat many other diseases, such as cancer and autoimmune diseases, including systemic lupus erythematosus, type I diabetes mellitus, rheumatoid arthritis, and multiple sclerosis. AIDS research also contributes to the prevention of other infectious diseases and has provided a new paradigm for treatment of viral diseases.

The great advances made in the treatment and prevention of the opportunistic infections that complicate HIV disease have had an impact on the care of patients with other immunodeficiency states who are susceptible to many of the same pathogens. This research effort has enhanced the care of cancer patients, patients who have received immunosuppressive therapy for bone marrow or solid organ transplants or for the treatment of diseases caused by heightened immune responses. HIV research has assisted in identifying new infectious agents that may be responsible for malignancies, such as the recent discovery of the etiologic agent of Kaposi's sarcoma. Such approaches may help to identify other oncogenic agents. HIV research has led to a better understanding of the mechanisms by which infectious agents and inflammatory cells gain access to the brain. This research has valuable implications for the study of Alzheimer's disease, dementia, multiple sclerosis, neuropsychological disorders, encephalitis, and meningitis.

Efforts to develop drugs for the treatment of HIV has accelerated the development of methods of rational drug design using sophisticated techniques of structural biology and advanced computer imaging methods. These advances will be of great importance in the design of drugs for virtually all disorders. Comparative clinical trials of poxvirus vectors and of vaccine adjuvants in HIV vaccine candidates have supported safety information for cancer vaccines. Research on HIV-related wasting has provided important information for research on nutritional disorders, metabolic abnormalities and gastrointestinal dysfunctions.

The Office of AIDS Research

The Office of AIDS Research, within the Office of the Director, NIH, has overall responsibility to plan, coordinate, evaluate, and fund the AIDS research program of the NIH, which is carried out in each Institute, Center, and Division (ICD), consistent with its individual mission. To formulate this AIDS research plan, the OAR enlisted the aid of distinguished scientists, with expertise both in AIDS research and from related disciplines. A unique and inclusive process was utilized, involving the NIH Institute and Center Directors; NIH intramural and extramural scientists and program managers; scientists and researchers from other government agencies, academia, foundations, and industry; HIV-infected men and women; and other community representatives. This diverse and eminent group of experts reached a consensus regarding the scientific priorities and opportunities in HIV-related research, which is reflected in the *FY 1997 Plan for HIV-Related Research* and in this FY 1997 request.

In addition, utilizing expertise of non-government scientists and AIDS community representatives, OAR has undertaken a major comprehensive evaluation, now nearing completion, to review and assess each of the components of the NIH AIDS research endeavor. The goal of the evaluation is to determine whether those components are appropriately designed and coordinated to answer the critical scientific questions to lead to better treatments, prevention, and a cure for AIDS. The recommendations of this important review will be presented in early April, 1996.

AIDS Loan Repayment Program

In FY 1995 the NIH awarded \$618,060 to twenty-four individuals under its AIDS Research Loan Repayment Program (AIDS-LRP). Awards were made to twenty-two health professionals, representing fifteen recipients who entered into one-year renewal contracts and seven researchers who entered into initial two-year contracts. The awardees agreed to conduct AIDS research as NIH employees, while the NIH agreed to provide repayment toward their educational debt, subject to a maximum of \$20,000 annually. In addition to educational loan repayments, the AIDS-LRP provides Federal tax reimbursements at the rate of 39 percent of loan repayments made as compensation for the increased tax burden resulting from the receipt of loan repayments. For FY 1996, the AIDS-LRP will award 15 contracts to 10 individuals entering into initial two-year contracts, and five entering into renewal contracts, at a cost of \$695,000.

In FY 1997, the request includes \$973,000 for the AIDS LRP to award contracts to 15 initial two-year recipients and 5 one-year renewal contracts.

The NIH AIDS Research Program

The NIH HIV-related research effort is divided into five major scientific categories: natural history and epidemiology; etiology and pathogenesis; therapeutics; vaccines; and behavioral and social sciences research. These research programs are conducted both through the NIH-sponsored programs of grants and contracts at major universities, research institutes, and small science-oriented businesses and in the NIH intramural research programs, mainly located in Bethesda and Frederick, Maryland. Dividing the AIDS science effort by subject is critical for research planning, but such categorization has not had the effect of insulating these fields of research from one another. Rather, these areas are inextricably linked and many research projects represent interdisciplinary approaches that deal with more than one of these areas. Similarly, although the extramural and intramural research efforts are supported by different funding mechanisms, they represent a single overall endeavor. Intramural and extramural research groups often collaborate on specific AIDS research projects. Two additional components provide important research resources to these efforts: training and infrastructure, and information dissemination.

Scientific Opportunities and Priorities

A number of new and exciting research advances provide optimism and open new areas for investigation. For example, a new class of drugs, the protease inhibitors, used in combination with other antiretroviral therapies, are now completing trials. One such drug has shown promising clinical results. When used in combination with reverse transcriptase inhibitors, protease inhibitors have remarkably diminished the amount of HIV in an infected individual. NIH-supported research has shown that zidovudine (AZT) can dramatically reduce the risk of transmission of HIV infection from a pregnant woman to her child. Effective treatments for HIV-related opportunistic infections can prolong and improve the quality of life of people with AIDS. More sensitive and reliable measurements of viral load and viral burden have been shown to be more accurate indicators of the antiviral activity of potential therapeutic agents. The impact of these new techniques will permit physicians to better tailor treatments for their patients and allow them to more closely monitor the benefits of therapies. These advances in turn provide new opportunities for investigation.

AIDS research has provided a deep knowledge of the molecular virology of HIV. This work, while not yet matched in depth by our grasp of the means through which infection leads to disease and how it induces immune deficiency, has, nonetheless, provided us with unique insights into the virus and its pathogenesis. Yet, we lack an effective preventive vaccine, and new and better antiviral agents are critically needed. Our understanding of mechanisms to modify risk-taking behavior is still very limited. We do not yet understand many aspects of the interaction between the virus and the infected individual.

The NIH AIDS research budget request is framed on the following scientific priorities:

- A rededication to fundamental science;
- A vigorous therapeutic research program, emphasizing both drug discovery and an efficient clinical trials system, with additional emphasis on increased participation of women, minorities, and other underrepresented populations;
- A stronger effort to develop new vaccines and to bring them to clinical trial as soon as possible; and
- An emphasis on prevention, including enhanced studies of risk-taking behavior and the development of strategies to avert infection, such as microbicides, female-controlled barriers and STD treatment and prevention.

The FY 1997 budget requests funds to support these critical areas of scientific opportunities, summarized in the following categories:

Natural History and Epidemiology

The NIH conducts studies to examine the transmission of HIV and the progression of HIV-related disease, including opportunistic infections, malignancies, neurological manifestations, wasting, and other sequelae. Epidemiologic research prospectively studies cohorts of HIV-infected individuals and healthy individuals who are at risk of infection. Examples of such research include the study of sexual transmission in specific populations; the study of the natural history of HIV-related disease in women, men, adolescents, and children; the study of transmission from mother to infant; and the study of behavior relative to the risk of transmission of HIV.

Studies of HIV disease progression are critical for determining how HIV causes destruction of the immune system and subsequent illness. These studies, performed in the United States as well as in other countries that may exhibit different patterns of the epidemic, afford scientists the opportunity to describe the biologic, psychological, clinical, socioeconomic, and medical-care-access consequences of HIV infection and HIV-associated disease. Persons enrolled in natural history types of studies are not denied access to treatments for HIV-associated conditions; rather, information on their treatments is combined with other clinical and psychosocial information to assess HIV-associated outcomes.

By linking ongoing natural history studies to basic virologic and immunologic research, new insights will be gained in targeting populations at risk for specific HIV-related outcomes and in developing new strategies for treatment and prevention, including vaccines. An important area of investigation, the study of long-term non-progressors, can reveal critical information that will assist in the development of vaccines and therapies for AIDS. Similarly, studies of persons who remain uninfected despite repeated exposures to HIV will yield new insights into how the immune system blocks infection.

New challenges and scientific opportunities in this area require investigation. Study is needed of new HIV strains and subtypes in the United States that may impact transmission rates and disease progression. NIH has placed high priority on studies focused on women and AIDS and to characterizing clinical manifestations of HIV specific to women. For example, adolescent females exposed to HIV and other sexually transmitted infections may be at higher risk of infection because of the immaturity of the cells of the genital tract. Further studies are needed to better understand HIV infection among adolescents. Research to develop chemical and barrier methods, including topical microbicides, is critical to help women prevent transmission of HIV and other sexually transmitted infections.

Etiology and Pathogenesis

The NIH will rededicate its efforts to basic research, the foundation that will support the entire AIDS research enterprise. In the quest for vaccines to prevent HIV infection, and better drugs to contain the infection and treat the opportunistic infections, tumors and other manifestations of a dysfunctional immune system, a better understanding is needed of how HIV infection is established and what causes the profound immune deficiency and terrible complications that accompany infection. What role do the specific products of HIV--the viral genes and their protein products--play in the viral life cycle of individual cells and within the body of infected individuals? How is HIV transmitted between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous and other organ systems that HIV afflicts? What host factors and cofactors influence the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies and opportunistic infections that characterize AIDS? These outstanding questions define the central contemporary issues encompassed within the area of etiology and pathogenesis research.

Since the initial isolation of HIV in 1983 and its identification as the causative agent of AIDS shortly thereafter, tremendous progress has been made in understanding the genetic structure and variability of the viral genome, critical aspects of the virus life cycle--the process by which the virus reproduces--and the functions of essential viral gene products. The knowledge that has emerged from basic research in these areas provided the foundation for all efforts to develop effective therapies to treat HIV infection.

Progress in these areas, much of it fueled by support provided by the NIH, continues at a rapid pace. Indeed, it is likely that more is now known about the fundamental biology of HIV than any other virus that causes disease in humans, yet much more remains unknown. The process of developing new drugs based upon the study of the fundamental properties of the relevant target of drug action is referred to as rational drug design. The basic research knowledge that represents the foundation of the concept of rational drug design emerged, in large part, from basic research supported by the NIH over a number of years. Although the potential benefits of this approach to drug development have yet to be fully realized, it will have applications to all aspects of human health and disease. It is likely that the effort to develop effective therapies to treat HIV infection and its associated conditions will provide a critical proving ground for the concept of rational drug design, and a source of great experience for the refinement and advancement of its methods. Already, new extremely potent antiviral drugs have been developed using basic research results concerning the HIV life cycle. These drugs, which will soon be available, promise to improve significantly the quality and quantity of life for HIV-

infected individuals. The derivation of these drugs would not have been possible without the elucidation of the structure and function of the critical enzymes, termed reverse transcriptase and protease, that HIV requires to reproduce itself.

The challenge remains to develop even more effective treatments for HIV infection. The inherent ability of HIV to develop resistance to antiviral drugs must be overcome. This will require continued research into all of the constituent structural and functional products of HIV. Continued progress in the definition of the intricate details of the virus life cycle, both within individual cells and within infected people, will permit the identification of new targets for the development of antiviral drugs and definition of the most effective ways to use them. Future developments in this area will continue upon the model that was used, and proven effective, in the development of all available HIV therapeutics; a cooperative endeavor in which NIH-funded scientists conduct basic research into viral functions and the pharmaceutical industry applies their expertise in drug development once sufficient basic information is available to support a "rational" developmental effort.

While the fundamental principles of the HIV life cycle have been defined in an expeditious fashion, insights into how HIV replicates, persists and causes disease in infected people have been more difficult to obtain. However, the concerted efforts on this issue by numerous NIH-sponsored investigators are now yielding impressive discoveries that are advancing our understanding of the disease process. The development and functioning of the human immune system has been the focus of significant interest and scrutiny, and a topic about which great discoveries have emerged. However, the fundamental complexity of the immune system has also provided an obstacle for rapid research progress in elucidating the pathogenesis of AIDS. It is a significant challenge to understand the normal functioning of the immune system while at the same time defining the mechanisms by which HIV infection disrupts it. Yet, this precise challenge has also created novel opportunities to learn important general lessons about how the immune system operates in both health and disease. Better understanding of the normal functioning of the immune system will be necessary if we are to understand the pathogenesis of AIDS. Likewise, a better understanding of the pathogenesis of AIDS will yield important insights into the normal immune system and how it may also fail in circumstances of autoimmune diseases or common infections and malignancies that are seen in persons not infected with HIV.

The challenge of understanding HIV infection and disease also represents an extraordinary example of how the biology of other infectious diseases may be studied in the future. Never before has the behavior of an infectious organism within an infected human been examined in such detail. To conduct this type of investigation, new research tools are required to facilitate sensitive, high-resolution analyses. The amount of virus present in an infected person must be

determined, and its level of replication and consequent damage measured. The need to understand HIV infection has driven technological developments in this area, and much of this effort has been fueled by NIH support.

The recent development of powerful tools to monitor the location and extent of HIV replication within infected persons have illuminated critically important details of how HIV infection leads to AIDS. Application of these new tools has revolutionized our understanding of the extent of HIV replication that takes place in infected people, and how virus replication is directly linked to the destruction of T cells and consequent immune system compromise. The broad outlines of the pathogenic mechanisms of HIV disease are now known, but the precise details of the process await definition. An improved understanding of these issues is necessary to permit definition of the optimal ways to use therapies to treat the primary HIV infection and its associated opportunistic complications.

While significant progress has been made in understanding HIV disease and developing more effective treatments, a vaccine to prevent HIV infection remains an elusive goal. Due to the unique features of HIV infection, it is considered unlikely that an effective HIV vaccine will emerge from the same type of empirical developmental efforts that have produced many of the available, effective vaccines such as those to prevent polio virus or measles virus infection. A much better understanding of the mechanisms of transmission of HIV between individuals and the processes by which the infection becomes established and persists is essential. Likewise, improved understanding of the nature of the immune response that contains, albeit temporarily, the replication of HIV and its resulting damage in infected persons, is necessary. The NIH is the major sponsor of research in these critical areas worldwide. Without a strong commitment to basic research into these questions, an effective HIV vaccine will likely remain an unrealized goal rather than a potent intervention to protect the public health.

The NIH has rededicated its efforts to basic research to meet these and other challenges. OAR will increase the resources available for support of investigator-initiated research and will encourage a broader pool of basic scientists, particularly immunologists and virologists, to join in this effort.

Therapeutics

The largest investment of AIDS research dollars is in the area of therapeutics. NIH-sponsored studies are actively pursuing the discovery and development of potential therapies for the prevention, early intervention, and treatment of HIV infection and its sequelae. Two approaches are being taken for the identification of potential antiretroviral agents, including targeted drug development that utilizes structural biology techniques to aid in the design of drugs and drug screening of synthetic and natural products for anti-HIV activity. The NIH sponsors intramural and extramural clinical trials of these potential therapeutic agents in single- or multi-

drug regimens to demonstrate drug safety and efficacy for the control and treatment of HIV infection and its accompanying OIs and malignancies in individuals of all ages. Innovative new therapies for immune reconstitution and a variety of gene therapy approaches to render cells resistant to HIV are being actively developed.

In the area of drug discovery, efforts to intercede in the viral life cycle have focused primarily on agents directed against the HIV reverse transcriptase and the HIV protease. Five reverse transcriptase inhibitors and one protease inhibitor are currently approved by the U.S. Food and Drug Administration for the treatment of HIV infection. Additional protease inhibitors are now completing the development process.

NIH will place special emphasis on the development of therapies based on new molecular targets in order to broaden the arsenal of weapons against the virus. The recent solution of the three-dimensional structure of the integrase of HIV-1 marks an important step toward the development of agents that may inhibit this critical viral enzyme, potentially providing an additional class of antiretroviral agents. The development of additional classes of drugs will require a more detailed understanding of HIV regulatory proteins and of the less well-studied accessory proteins as well as the design of biologically relevant screens for inhibitors of these gene products.

The development of novel approaches based on the latest understanding of the pathogenesis of the disease is a research priority. Such studies can provide information about the virological and immunological aspects of HIV disease *in vivo* by answering basic scientific questions within the framework of a clinical study. Similarly, studies of immune-based therapies may provide both new therapeutic approaches to HIV disease and clues to elucidating its pathogenesis. Other novel and innovative approaches currently in various stages of development by industry and academia include gene therapy and cell reconstitution therapy.

Therapeutic successes against HIV itself have been real, but limited. The oldest drug in the armamentarium, zidovudine, can prevent transmission of the virus from mother to infant, where it can reduce that rate by two-thirds. This is a landmark research accomplishment in the prevention of HIV among newborns. The administration of zidovudine with other reverse transcriptase inhibitors has now been shown to confer a survival benefit on HIV infected individuals. The task before us in the coming years is to deepen the magnitude of viral suppression, improve immunological and clinical benefit, and prolong the limited clinical efficacy of these initial antiretroviral agents. Preliminary results with protease inhibitors are very encouraging.

HIV-infected individuals are living longer with a better quality of life now than they did a decade ago. Indeed, the survival time of people with AIDS has doubled, largely due to advances in the treatment and prevention of opportunistic infections. There are currently 31 drugs licensed

for the treatment of HIV infection and its associated opportunistic infections and malignancies. These have been among our greatest successes in AIDS research thus far, and they have provided tangible benefits for people living with the disease.

While there have been important successes against some opportunistic pathogens, other HIV-associated infections and cancers present us with new challenges, including, for example, cryptosporidium and microsporidium, Kaposi's sarcoma, non-Hodgkin's lymphoma, and progressive multifocal leukoencephalopathy. Further, in this era of increasing antibiotic resistance, many common microbes once thought vanquished are returning with a vengeance. A particularly concerning example is the appearance of multidrug-resistant tuberculosis. To address these critical needs, NIH will intensify efforts to discover and develop new anti-infectives and novel antineoplastic agents.

The NIH AIDS clinical research infrastructure is composed of many networks that grew rapidly and independently of each other in the context of a public health emergency but in the absence of a broad plan for clinical research. They now receive a considerable fraction of the total NIH AIDS research budget. A more complete, coherent, and cost-effective clinical research effort is necessary and possible. These networks require better coordination; such coordination can provide the means for adequately testing new and existing agents and, at the same time, make resources available to other areas. The NIH has the unique capability of conducting studies to evaluate drugs from different manufacturers as well as to support clinical investigations of agents that small biotechnology companies are not able to financially support by themselves.

Additional biomedical and clinical research is needed to better understand dosing, drug formulations, pharmacokinetics, drug interactions, and toxicity issues associated with compounds administered singly as well as in multi-drug combinations. Furthermore, the identification of multi-drug combinations that can be administered over extended periods of time without the development of drug-resistance is important. NIH will continue to support activities in these areas.

While significant progress has been made in the development of drugs against HIV and its associated sequelae, many scientific and clinical questions still remain. While the number of agents in the arsenal against HIV and many of the opportunistic infections associated with this disease is increasing, new potential compounds against molecular targets and innovative approaches are needed. Accomplishing this goal will require industry's further involvement and collaboration with federally-sponsored research efforts.

Vaccines

Our greatest hope for the eradication of HIV lies in the development of effective preventive vaccines. Indeed, in many parts of the world, vaccines are the only realistic way to

deal with the epidemic. Phase I/II trials are currently under way and Phase III field trials of two gp120-based vaccines are now planned under WHO auspices in collaborative ventures with vaccine manufacturers and the public health authorities in Thailand. These vaccine candidates were also considered for such testing within the United States. An NIH advisory committee judged that U.S. trials were not yet warranted because of the concern about the limited ability of these vaccines to stimulate production of antibody. These alternative decisions are, in part, a reflection of differences in the nature of the epidemic in different parts of the world and of the potential value of partially effective vaccines in these different settings. The possibility that the available gp120-based vaccines may have only partial or limited effectiveness has forced NIH to recognize the urgency of the development of second-generation HIV preventive vaccines with enhanced immunogenicity. This effort must be based on the latest knowledge about the virus and the immune response it evokes. Large-scale testing of vaccines will proceed in the United States when reliable scientific evidence suggests that our new candidates have a reasonable degree of promise to induce both antibody and CTL response.

NIH will increase support for studies of the mechanisms of immunological resistance to infection with HIV and related lentiviruses. Work is now proceeding on several unique cohorts of individuals that may hold important clues in this regard. In Kenya and Senegal as well as the Gambia, groups of women who, despite repeated apparent exposure to HIV, have resisted infection are being carefully analyzed. Health care workers who, despite exposure to the virus have remained uninfected but do show evidence of immune response to viral antigens, are also being studied. Recent studies of at-risk partners of HIV-infected individuals from two U.S. sites have shown that cells from some individuals are resistant to HIV, particularly at low virus doses. These exposed but uninfected individuals may have acquired a form of protective immunity; understanding the nature of this immunity and how it is induced can provide insight into what is required for effective vaccine-based prevention. New information from HIV transmission studies indicates that it may be easier to protect against a mucosal route of transmission, which appears to be relatively inefficient.

An immune response that slows progression of an established infection may be very different from one that protects against initial infection with the virus. Long-term non-progressors, may share unique immune responses that are particularly potent against the virus once infection has been established. The analysis of these responses promises to provide important clues for us in the effort to understand the characteristics of an immune response that is effective in HIV-positive individuals.

Animal models, particularly the SIV-infected macaque, will be important in understanding the details of pathogenesis and in establishing the nature of protective immunity. It is particularly important to understand the nature of the immunity to a fully virulent SIV that is induced by vaccination with attenuated viral mutants. It is critical to determine what mutations will permit sufficient viral replication to induce robust immunity without long-term safety risks.

NIH is supporting studies of these immune responses and will take an active role in determining whether attenuated viruses can be developed that are sufficiently safe to warrant serious consideration as vaccine candidates. Risk/benefit ratios of an attenuated virus vaccine will vary depending on infection rates and other considerations. An attenuated virus vaccine may be entirely appropriate in certain settings but less appropriate or unacceptable in others.

Despite setbacks in subunit vaccines for HIV, new data from passive immunity in primate models, cross neutralization of different virus clades, and immunological studies from at-risk cohorts strongly support a renewed commitment to vaccine research that will produce broad recognition of different types of the virus with both cellular and humoral immune responses.

Behavioral Research

NIH AIDS research in the behavioral and social sciences has and will continue to focus on three key areas: improving primary prevention of HIV infection through behavior change interventions; developing the basic science that underlies behavior change interventions; and addressing the individual and societal consequences of HIV and AIDS. Cutting across these areas is a continued commitment to improving the methodologies employed in behavioral and social sciences research, and to better link research with communities most affected by HIV and AIDS.

Much has been learned and accomplished in the area of HIV/AIDS prevention through behavior change interventions. Theory-driven intervention models have been developed and employed by researchers supported by NIH, and have demonstrated that preventive interventions work, even among hard-to-reach populations. Marked changes in sex and drug using behaviors have been observed among such groups as rural gay men, out-of-treatment injection drug users, and homeless and runaway youth. At this point, most behavior change interventions have been tested in small groups, in a limited number of communities, and over relatively short periods of time. It is now important to further replicate and refine these interventions, to add new ones, to test their effectiveness on a broader scale, over longer periods of time, and targeted to specific populations taking into account their cultural and social contexts.

The focus of basic research in the behavioral and social sciences is to gain a thorough understanding of the psychological, social, and cultural factors that contribute to HIV risk and protective behavior. NIH-supported researchers are investigating the fundamental mechanisms of risk behavior--neurobiological factors, psychological factors, social and cultural factors related to norms and values about sexuality, drug use, and HIV/AIDS itself. While advances have been made in this area by researchers supported by NIH, much more remains to be learned. Basic behavioral and social science research in these areas will have implications not only for HIV and AIDS prevention, but for health promotion and disease prevention in a range of other areas of interest to NIH.

NIH-supported researchers are beginning to study the social and cultural impact of the pandemic, examining the implications of the stigma of HIV/AIDS on the care and treatment of infected persons; the social and psychological status of orphaned children whose parents have died from AIDS; and the impact of HIV/AIDS on health care systems and economies of communities that have been most affected by the epidemic. In addition, techniques for improving our ability to estimate in quantitative terms the success of behavioral interventions are in a relatively early state of development, but an increasing number of researchers in mathematical modeling and biostatistics are entering the field. Continued support should see further refinement in such methodologies that will produce better estimates for projecting the course of the epidemic in different populations and the possibilities for stemming it through specific interventions. In turn, this will improve our ability to determine the most successful interventions and to apply resources accordingly.

Conclusion

AIDS research has reached an important juncture. Important progress has been made in our fight against this most formidable foe; a preventive vaccine against infection and therapies with sustainable effect are still beyond our grasp. The most important scientific opportunities lie in our insight into the virus and the disease that it causes. With this comprehensive AIDS budget request, NIH is redirecting and refocusing efforts to guide research that will lead to our ultimate goal--the elimination of AIDS from our world.

DHHS - National Institutes of Health
FY 1997 AIDS Budget by Mechanism
(dollars in thousands)

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Research grants:						
Research projects:						
Noncompeting.....	1231	\$446,604,000	1372	\$482,192,000	1410	\$510,377,000
Administrative supplements.....	(89)	5,558,000	(47)	3,583,000	(47)	3,648,000
Competing:						
Renewal.....	125	42,219,000	116	60,308,000	161	64,741,000
New.....	320	90,141,000	285	102,681,000	375	114,272,000
Supplements.....	49	16,978,000	46	14,925,000	49	18,730,000
Subtotal, competing.....	494	149,338,000	447	177,914,000	585	197,743,000
SBIR/STTR.....	83	13,203,000	104	16,765,000	134	21,279,000
Subtotal, research projects.....	1808	614,703,000	1923	680,454,000	2129	733,047,000
Research Centers:						
Specialized/Comprehensive.....	32	46,113,000	31	53,755,000	31	53,560,000
General Clinical Research.....		31,690,000		33,661,000		33,661,000
Biomedical Research Technology.....		854,000		1,854,000		1,739,000
Biological Models and Materials Research.....	12	23,076,000	11	22,780,000	11	22,990,000
Research Centers in Minority Institutions.....		6,016,000		6,507,000		6,507,000
Subtotal, Research Centers.....	44	107,749,000	42	118,557,000	42	118,457,000
Other research:						
Research career programs.....	128	10,962,000	135	11,952,000	137	12,361,000
Cooperative Clinical Research.....	4	9,250,000	4	10,634,000	4	8,885,000
Biomedical Research Support.....	1	659,000		1,659,000		1,659,000
Minority Biomedical Research Support.....		547,000		585,000		585,000
Other Research.....	40	13,336,000	36	13,222,000	35	13,196,000
Subtotal, other research.....	173	34,754,000	175	38,052,000	176	36,686,000
Total, research grants.....	2025	757,206,000	2140	837,063,000	2347	888,190,000

Research Training:						
Individual awards:						
Noncompeting.....	43	959,000	52	1,297,000	43	1,097,000
Competing.....	44	1,068,000	34	840,000	44	1,084,000
Subtotal, individual.....	87	2,027,000	86	2,137,000	87	2,181,000
Institutional awards:						
Noncompeting.....	520	12,715,000	578	14,671,000	568	14,747,000
Competing.....	197	5,388,000	140	4,026,000	144	4,039,000
Subtotal, institutional.....	717	18,103,000	718	18,697,000	712	18,786,000
Total, training.....	804	20,130,000	804	20,834,000	799	20,967,000
Research and development contracts						
SBIR/STTR.....	294	267,979,000	309	277,903,000	293	266,399,000
	(3)	(1,426,000)	(3)	(534,000)		
Intramural Research						
Research management and support.....		200,917,000		185,924,000		172,604,000
Subtotal, ICDe.....		60,555,000		56,340,000		55,837,000
		1,306,787,000		1,378,064,000		1,403,997,000
National Library of Medicine						
Office of the Director.....		2,694,000		3,162,000		3,311,000
Buildings and Facilities.....		24,394,000		26,598,000		24,600,000
Total.....		1,333,875,000		1,407,824,000		1,431,908,000
Clinical Trials						
		(353,297)		(362,924)		(360,258)

Note: FTEs associated with HIV/AIDS Research Activities are included in the justifications of the Institutes, Centers and Divisions.

National Institutes of Health
Office of AIDS Research

Dollars in thousands

	FY 1993	FY 1994	FY 1995	FY 1996 Estimate	FY 1997 Estimate	Change
National History and Epidemiology	\$162,513	\$176,227	\$192,624	\$205,812	\$203,285	-\$2,527
Etiology and Pathogenesis	228,076	336,925	344,303	382,903	400,182	+17,279
Therapeutics	431,392	458,085	462,929	472,944	470,042	-2,902
Vaccines	81,544	110,611	100,399	109,533	116,132	+6,599
Behavioral Research	136,664	159,783	170,984	174,077	180,238	+6,161
Training and Infrastructure	26,240	39,192	46,483	44,643	44,335	-308
Information Dissemination	5,028	15,648	16,153	17,912	17,694	-218
Total	1,071,457	1,296,471	1,333,875	1,407,824	1,431,908	+24,084

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Summary of Changes

1996 Estimated budget authority.....	\$1,407,824,000
1997 Estimated budget authority.....	1,431,908,000
Net Change	+24,084,000

	1996 Current Estimate Base		Change from Base	
	Poa. (FTE's)	Budget Authority	Poa. (FTE's)	Budget Authority
Changes:				
A. Built-in				
1. Intramural				
a. Within grade increases.....		\$42,961,000		+\$658,000
b. Annualization of January 1996 pay increase.....		42,961,000		+275,000
c. January 1996 pay increase.....		42,961,000		+973,000
d. Increase in Unemployment compensation.....		42,961,000		+9,000
e. Increased cost for centrally furnished services.....		47,673,000		-296,000
f. Increased cost for Service and Supply Fund.....		30,493,000		+723,000
g. Increased cost of laboratory supplies, materials and other expenses.....		64,797,000		+1,535,000
Subtotal.....				+3,877,000
2. Research Management and Support				
a. Within grade increases.....		\$25,345,000		+\$385,000
b. Annualization of January 1996 pay increase.....		25,345,000		+162,000
c. January 1996 pay increase.....		25,345,000		+573,000
d. Increase in Unemployment compensation.....		25,345,000		+3,000
e. Increased cost for centrally furnished services.....		7,113,000		-86,000
f. Increased cost for Service and Supply Fund.....		7,642,000		+221,000
g. Increased cost of laboratory supplies, materials and other expenses.....		16,240,000		+471,000
Subtotal.....				+1,729,000

Summary of Changes (cont)

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.....	1,372	\$482,192,000	+38	+28,185,000
b. Administrative supplements.....	(47)	3,583,000	—	+65,000
c. Competing.....	447	177,914,000	+138	+19,829,000
Subtotal.....	1,819	663,689,000	+176	+48,079,000
SBIR/STTR.....	104	16,765,000	+30	+4,514,000
Total.....	1,923	680,454,000	+206	+52,593,000
2. Research centers.....	42	118,557,000	—	-100,000
3. Other research.....	175	38,052,000	+1	-1,366,000
4. Research training.....	804	20,834,000	-5	+133,000
5. Research & development contracts.....	309	277,903,000	-16	-11,504,000
6. Intramural research.....		185,924,000		-17,197,000
7. Research management and support.....		56,340,000		-2,232,000
8. Office of AIDS Research.....		26,598,000		-1,998,000
9. National Library of Medicine.....		3,162,000		+149,000
Subtotal Program.....				+18,478,000
Total changes.....				+24,084,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

AIDS Funding by Institute and Center

ICD	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
NCI	\$217,735,000	\$225,790,000	\$220,539,000
NHLBI	55,485,000	57,925,000	58,115,000
NIDR	11,733,000	12,309,000	12,318,000
NIDDK	10,752,000	11,735,000	11,948,000
NINDS	22,741,000	23,807,000	23,950,000
NIAID	557,766,000	596,018,000	624,368,000
NIGMS	24,664,000	26,135,000	27,050,000
NICHD	58,667,000	60,713,000	60,209,000
NEI	8,606,000	9,125,000	9,135,000
NIEHS	5,745,000	6,051,000	6,028,000
NIA	1,715,000	1,785,000	1,824,000
NIAMS	3,879,000	4,039,000	3,972,000
NIDCD	1,552,000	1,650,000	1,726,000
NIMH	89,351,000	93,556,000	93,056,000
NIDA	147,347,000	153,331,000	154,311,000
NIAAA	9,741,000	10,135,000	10,334,000
NINR	4,577,000	4,896,000	5,015,000
NCRR	64,630,000	68,370,000	68,255,000
NCHGR	993,000	1,000,000	2,087,000
FIC	9,108,000	9,694,000	9,757,000
Subtotal, ICDs	1,306,787,000	1,378,064,000	1,403,997,000
NLM	2,694,000	3,162,000	3,311,000
OD	24,394,000	26,598,000	24,600,000
Bldg. and Fac.	---	---	---
Total, NIH	1,333,875,000	1,407,824,000	1,431,908,000

**DHHS-National Institutes of Health
AIDS By Functional Category**
(dollars in thousands)

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Category	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
I. BASIC SCIENCE RESEARCH:			
A. Biomedical Research:			
1. HIV and HIV genome	\$98,863	\$107,416	\$111,749
2. Immunology	148,542	167,719	178,431
3. Blood/Blood products	12,059	16,378	18,362
4. Diagnostic methods/reagents development	7,585	7,223	8,788
5. Animal models and related studies	28,741	34,473	35,122
SUBTOTAL, Biomedical Research	297,790	333,209	350,432
B. Neuroscience and Neuropsychiatric Research	47,612	48,825	48,996
C. Behavioral Research:			
1. Mechanisms of behavior and behavior change	22,411	23,148	24,464
2. Prevention of high-risk behaviors	147,221	148,280	148,230
SUBTOTAL, Behavioral Research	169,632	171,438	172,694
D. Therapeutic Agents:			
1. Development	206,718	218,682	230,305
2. Clinical Trials	286,278	293,150	281,144
SUBTOTAL, Therapeutic Agents	494,995	511,832	511,449
E. Vaccines:			
1. Development	75,227	77,127	82,508
2. Clinical Trials	38,608	44,421	45,223
SUBTOTAL, Vaccines	114,835	121,548	127,732
F. Research Enhancement:			
1. Training	24,307	25,833	26,409
2. Construction (Extramural)	190	200	200
SUBTOTAL, Research Enhancement	24,497	26,033	26,609
TOTAL, BASIC SCIENCE RESEARCH	1,149,361	1,213,985	1,238,912
II. RISK ASSESSMENT AND PREVENTION:			
A. Surveillance:			
1. Diseases associated with HIV	4,066	3,140	2,925
2. HIV surveys (incidence, prevalence)	31	33	33
3. Knowledge, attitudes, behaviors	432	600	613
SUBTOTAL, Surveillance	4,529	3,773	3,571
B. Population-Based Research: Natural History, Transmission, Risk Factors:			
1. Transmission:			
a. Sexual	23,564	26,844	26,635
b. Intravenous drug abusers	2,951	3,619	3,657
c. Hemophilia populations	1,444	1,673	1,672
d. Blood recipient/donor studies	9,492	805	4,080
e. Perinatal infection	25,858	30,838	26,220
f. Occupationally related	112	139	140
g. Other/Miscellaneous	5,928	7,396	5,274
SUBTOTAL, Transmission	69,149	71,114	69,678
2. Natural history and cofactors	89,456	107,923	108,771
SUBTOTAL, Population based research	168,605	179,037	178,449

**DHHS-National Institute of Health
AIDS By Functional Category**
(Return to Summary)

Category	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
C. Information and Education/Preventive Services:			
1. High risk or infected persons:			
a. Health education/risk education	1,038	691	700
b. Counseling, testing, partner notification	97	101	101
c. Perinatal AIDS prevention projects	0	0	0
d. HIV prevention among drug abusers	695	705	705
e. Special projects:			
(1) Conference of Mayors	0	0	0
(2) HIV-related tuberculosis demonstration projects	0	0	0
(3) National Hemophilia AIDS/HIV prevention project	0	0	0
(4) Community-based demonstration projects	0	0	0
SUBTOTAL, Special projects	0	0	0
SUBTOTAL, High-Risk or Infected Persons	1,830	1,497	1,506
2. Special Minority Initiatives	498	0	0
3. School and college aged youth:			
a. National efforts	0	0	0
b. State and local projects	0	0	0
c. Program development and training	0	0	0
SUBTOTAL, School and college aged youth	0	0	0
4. General Public and Special Programs:			
a. National:			
(1) Clearinghouse	0	0	0
(2) Hotline (general public)	0	0	0
(3) Treatment trials and therapy, information services	3,631	4,022	4,140
SUBTOTAL, National	3,631	4,022	4,140
b. Regional, state, and local	100	890	494
SUBTOTAL, Gen. Pub. and Spec. Prog.	3,731	4,712	4,634
5. Health-Care Workers and Providers:			
a. Education and training centers	610	663	663
b. Other types of training	122	141	142
SUBTOTAL, Health-Care Workers and Providers	732	804	805
6. Prevention Capacity Enhancement	0	0	0
SUBTOTAL, Information and education/preventive services	6,791	7,013	6,945
TOTAL, RISK ASSESSMENT AND PREVENTION.	179,925	189,823	188,965
IV. CLINICAL HEALTH SERVICES RESEARCH AND DELIVERY:			
A. Services	0	0	0
B. Health Services Grants	0	0	0
C. Construction	0	0	0
D. Research	4,589	4,016	4,031
TOTAL, CLINICAL HLTH SERV. RESCH AND DEL	4,589	4,016	4,031
V. PHS-WIDE ACTIVITIES:			
C. Construction (PHS Facilities)	0	0	0
OAR Discretionary Fund.....	0	0	0
TOTAL.....	1,333,875	1,407,824	1,431,908

DHHS - National Institutes of Health

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FY 1997 Congressional Justification

AIDS Budget by the FY 1997 Plan

(Dollars in thousands)

	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
I. Natural History and Epidemiology			
1. Develop & assess intervention strategies to reduce or prevent HIV transmission in both domestic & international settings.	\$56,071	\$53,574	\$55,610
2. Characterize the risk factors & mechanisms of HIV transmission in both domestic & international populations, with the goal of preventing transmission.	42,953	48,156	53,175
3. Elucidate the progression of HIV infection, from its earliest stages through long-term sequelae, with the goal of understanding, preventing, & treating those factors.	44,480	50,942	46,390
4. Undertake epidemiologic research to reduce or prevent the occurrence of opportunistic illness in HIV-infected persons.	9,599	9,903	10,720
5. Develop & evaluate new laboratory assays, behavioral methods, & statistical techniques for epidemiologic studies.	39,521	43,237	37,390
TOTAL	192,624	205,812	203,285
II. Etiology and Pathogenesis			
1. Delineate the cellular & molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction.	222,791	253,937	254,967
2. Delineate the molecular & cellular mechanisms of transmission & establishment of infection & their impact on disease progression.	16,022	21,480	30,253
3. Elucidate the etiologic factors & cofactors in the pathogenesis of AIDS-associated disease states. Enhance a bidirectional flow between basic & clinical observations & intervention programs on HIV-related complications & foster interdisciplinary collaborations.	102,715	104,734	112,136
4. Elucidate the etiology & pathogenesis of HIV-related disorders: gastrointestinal, renal, endocrine, cardiovascular, cutaneous, hematologic, oral, pulmonary, & other diseases.	2,775	2,752	2,826
TOTAL	344,303	382,903	400,182

III. Therapeutics

	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
1. Improve understanding of the structure & function of molecular targets in order to develop improved assays for such targets; conduct screening, discovery, & preclinical development of novel anti-HIV agents & strategies (such as gene transfer technology & interruption of transmission) directed to the virus and/or host cell, & foster activity by & in collaboration with industry.	158,300	152,481	156,748
2. Conduct clinical trials & develop new trial methodologies for the treatment of HIV infection. Trials should be designed in order to rapidly develop new therapeutic strategies, optimize clinical efficacy & proper use of available modalities, define factors that effect the success of therapeutic strategies (including the role of resistance), & advance our understanding of disease pathogenesis & progression.	150,698	157,266	145,436
3. Develop & evaluate strategies that will enhance, restore, and/or maintain the immune systems of HIV-infected individuals & extend our understanding of immunopathogenesis.	21,948	21,982	24,799
4. Discover, develop, & evaluate potential agents for prevention & treatment of HIV-associated OIs & other infections modified by HIV infection.	97,281	99,726	102,015
5. Develop, evaluate, & implement strategies for interrupting vertical transmission of HIV from mother to child & extend our understanding of perinatal transmission & the pathogenesis of early infection (treatment of children will be addressed in other objectives). [Note: The OAR Coordinating Committee on Therapeutics feels scientific objectives 3.5 through 3.7 are of equal weight in terms of scientific priorities.]	4,022	4,352	4,929
6. Discover, develop, & evaluate improved strategies for the treatment & prevention of HIV-associated malignancies & extend our understanding of the risk factors for & pathogenesis of such malignancies.	8,909	13,277	12,805
7. Develop strategies for assessing, preventing, & treating central & peripheral nervous system dysfunction in the course of HIV infection.	13,126	13,991	13,218
8. Develop & evaluate therapies for the treatment of serious HIV-associated complications, especially wasting syndrome & growth failure, as well as other disorders including hematologic, dermatologic, renal, metabolic, pulmonary, & oral manifestations.	8,645	9,869	10,092
TOTAL	482,929	472,944	470,042

IV. Vaccines

1. To increase scientific knowledge of host defense mechanisms leading to protection against HIV infection and disease.

FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
28,183	36,425	39,046

2. Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models, and foster collaboration with industry in the research and development of candidate vaccines.

38,395	36,390	40,829
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3. Select candidate vaccines or concepts suitable for Phase I and Phase II trials and conduct these trials.

18,904	20,917	20,891
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4. Identify mechanisms of protective immunity to HIV in newborns and infants and support the development of safe and effective immunologic strategies for preventing or controlling HIV infection in this population.

6,771	7,252	7,222
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5. Identify appropriate domestic and international populations and develop infrastructure and collaborations with government, communities, and industry necessary for ensuring adequate performance of Phase III efficacy trials.

8,146	8,549	8,144
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6. Select suitable vaccine candidates and support efficacy trials when appropriate criteria are met.

0	0	0
100,399	109,533	116,132

TOTAL**V. Behavioral and Social Science Research**

1. Support research to develop and evaluate social and behavioral interventions at the societal, community organizational, and individual levels to reduce HIV transmission by reducing HIV related risk behaviors and increasing protective behaviors. Multi-site and cross-national studies are encouraged.

53,466	55,221	65,235
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2. Support basic research to strengthen the understanding of determinants and processes that influence HIV-related risk behaviors and the consequences of HIV disease.

89,635	90,146	87,308
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3. Support research for the discovery, development and evaluation of strategies for preventing or minimizing the negative physical, psychological, cognitive, and social consequences of HIV, including stigmatization of persons with or at risk for HIV infection. Support research strategies for promoting effective health care utilization among persons with HIV infection.

26,910	27,693	26,823
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4. Support research to advance innovative quantitative and qualitative methodologies to enhance HIV behavioral and social science research.

873	1,017	872
170,984	174,077	180,236

TOTAL

	FY 1995 Actual	FY 1996 Estimate	FY 1997 Estimate
VI. Training and Infrastructure			
1. Provide both domestic and international training in biomedical and behavioral research on HIV.	26,296	27,545	27,429
2. Establish appropriate infrastructure for the conduct of HIV research domestically and internationally.	20,187	17,096	16,906
TOTAL	46,483	44,643	44,335
VII. Information Dissemination			
1. Support the effective dissemination and utilization of HIV/AIDS information to all constituent communities of the NIH.	15,202	16,836	16,485
2. Support research to identify existing gaps in communications approaches, identifying existing strategies that are effective, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant audiences.	655	756	726
3. Develop, implement, & evaluate mechanisms that promote coordination & collaboration on all current HIV/AIDS communication activities Federal groups.	296	320	483
TOTAL	16,153	17,912	17,694
OAR Discretionary Fund			
TOTAL, Funding by the Plan	1,333,875	1,407,824	1,431,908

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
AIDS

BUDGET AUTHORITY BY OBJECT

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$42,704,000	\$44,294,000	+\$1,590,000
Other than full-time permanent	5,852,000	9,143,000	+291,000
Other personnel compensation	2,236,000	2,266,000	+30,000
Special Personnel Services	4,220,000	4,347,000	+127,000
Total, Personnel Compensation	58,012,000	60,050,000	+2,038,000
Personnel Benefits:			
Civilian personnel benefits	13,634,000	14,078,000	+444,000
Benefits for former personnel	202,000	210,000	+8,000
Travel and transportation of persons	2,657,000	2,832,000	-25,000
Transportation of things	443,000	428,000	-15,000
Rental Payments to GSA	2,137,000	2,201,000	+64,000
Rental payments to others	876,000	825,000	-50,000
Communications, utilities, and miscellaneous charges	3,501,000	3,516,000	+15,000
Printing and reproduction	1,180,000	1,119,000	-61,000
Consulting services	3,976,000	4,170,000	+195,000
Other services	58,366,000	42,698,000	-15,768,000
Purchases from Govt Accts	107,449,000	106,480,000	-969,000
Operation & Maintenance of Facill.	28,582,000	29,151,000	+569,000
R&D Contracts	235,402,000	221,882,000	-13,520,000
Medical Care	556,000	539,000	-17,000
Operation & Maintenance of Equip.	1,588,000	1,547,000	-41,000
Subsistence & Support of Persons	0	0	0
Supplies and materials	23,903,000	23,838,000	-65,000
Equipment	7,279,000	7,310,000	+31,000
Lands and structures	0	0	0
Investments & Loans	0	0	0
Grants, subsidies, and contributions	857,697,000	909,167,000	+51,260,000
Insurance claims and indemnities	181,000	172,000	-9,000
Interest and dividends	5,000	5,000	0
Refunds	0	0	0
TOTAL OBLIGATIONS	1,407,824,000	1,431,908,000	+24,084,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1997 CONGRESSIONAL JUSTIFICATION
AIDS

PERSONNEL COMPENSATION & ADMINISTRATIVE COST

OBJECT CLASSIFICATION	FY 1996 Estimate	FY 1997 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	\$42,704,000	\$44,294,000	+\$1,590,000
Other than full-time permanent	8,852,000	9,143,000	+291,000
Other personnel compensation	2,236,000	2,266,000	+30,000
Special Personnel Services	4,220,000	4,347,000	+127,000
Total, Personnel Compensation	58,012,000	60,050,000	+2,038,000
Personnel Benefits:			
Civilian personnel benefits	13,634,000	14,078,000	+444,000
Benefits for former personnel	202,000	210,000	+8,000
Travel and transportation of persons	2,667,000	2,632,000	-25,000
Transportation of things	443,000	428,000	-15,000
Rental payments to others	875,000	825,000	-50,000
Communications, utilities, and miscellaneous charges	3,501,000	3,516,000	+15,000
Printing and reproduction	1,180,000	1,119,000	-61,000
Consulting services	3,977,000	4,172,000	+195,000
Other services	68,364,000	42,693,000	-15,771,000
Purchases from Govt Accts	79,636,000	78,808,000	-828,000
Operation & Maintenance of Facill.	105,000	105,000	0
Operation & Maintenance of Equip.	556,000	539,000	-17,000
Subsistence & Support of Persons	0	0	0
Supplies and materials	23,903,000	23,838,000	-65,000
TOTAL, AIDS	247,045,000	232,913,000	+14,132,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Significant Items in the House and Senate Appropriations Committee Reports1996 House Appropriations Committee Report LanguageItem

Department of the Army AIDS Research--The House in its report 104-209, page 80 stated,-- "The Appropriations Committee has transferred responsibility to NIH for primary support of the extramural AIDS research program presently funded by the Department of the Army; the Committee intends that NIH fund the continuation costs of this program. At the conclusion of the normal grant period, NIH will consider further funding of this research in the context of its entire AIDS research portfolio. The Committee expects NIH to support the Army research without interruption in fiscal year 1996. However, if NIH has concerns about funding some portion of this research activity, the Director may submit a reprogramming request to the Committee. The Committee expect research cooperation to continue between NIH and the Department of the Army."

Action Taken or To Be Taken

To maintain the Department of the Army AIDS research program, the House provided funding directly to the Department of the Army in the FY 1996 bill.

1996 Senate Report LanguageItem

Office of AIDS Research--The Senate in its report 104-145, page 115, stated "The NIH Office of AIDS Research (OAR) coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS Research program. Congress provided new authorities to the OAR to fulfill these responsibilities in the NIH Revitalization Act Amendments of 1993. The law mandates the OAR develop an annual comprehensive plan and budget for all NIH AIDS research and to prepare a Presidential bypass budget."

Action Taken or To Be Taken

The Office of AIDS Research, within in the Office of the Director, NIH has overall responsibility to plan, coordinate, evaluate and fund the AIDS research program of the NIH. Congress provided broad new authorities to the OAR to fulfill these responsibilities in the NIH Reauthorization Act Amendments of 1993.

The OAR is responsible for the development of the annual comprehensive planning and budgeting process for all NIH AIDS research, and for preparation of the Presidential by-pass budget. The OAR has completed the annual comprehensive plans and budget requests in FY 1996 and 1997 as well as the Presidential bypass budget. The plan developed in FY 1997 is the basis for the budget contained in this document.

The OAR has established and supports the efforts of six trans-NIH Coordinating Committees in the following areas: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; Behavioral Research; and Information Dissemination.

The OAR brought together hundreds of non-government scientists from both AIDS and AIDS-related fields along with Institute Directors and NIH scientists to construct the annual plan for AIDS research. This represents a consensus-building among NIH and non-NIH scientists to set the overall scientific directions and priorities that subsequently determine the resources allocated to meet these priorities.

An OAR Discretionary Fund was authorized to allow expeditious pilot funding to the Institutes and Centers for new scientific initiatives as well as rapid supplementary funding for scientific "break-throughs" or emergencies in ongoing research.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Authorizing Legislation

	<u>PHS Act/ Other Citation</u>	<u>U.S. Code Citation</u>	<u>1996 Amount Authorized</u>	<u>1996 Estimate</u>	<u>1997 Amount Authorized</u>	<u>1997 Budget Request</u>
Research and Investigation.....	Title IV Section 301		Indefinite	---	Indefinite	\$1,400,941,000
Office of AIDS Research.....	Title XXIII Section 2351			---	Authorization Pending	
Emergency Discre- tionary Fund.....	Title XXIII Section 2356		\$100,000,000	---	Authorization Pending	10,000,000
National Research Service Awards....	Section 487(d)		Such sums as necessary	---	Authorization Pending	20,967,000
				---		1,431,908,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Appropriation History

<u>Year</u>	<u>Budget Estimate 1/ to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u>
1995	\$1,379,052,000	\$1,337,606,000	\$1,337,606,000	\$1,335,421,000 2/ -1,851,000
1996	1,407,824,000		3/ 1,382,861,000	1,407,824,000 4/
1997	1,431,908,000			

1/ Includes all amounts associated with the National Institutes of Health AIDS Research Program.

2/ Excludes procurement reform, rent, and salary and expense reductions of \$2,185,000.

3/ The House did not provide separate funding for HIV/AIDS activities. The funds to support these activities are included in the appropriations of the Institutes and Centers.

4/ A regular appropriation for this account has not been enacted. The 1996 amounts included in this budget are based on comparable levels provided in three continuing resolutions: P.L. 104-91, P.L. 104-92, and P.L. 109-99.

WEDNESDAY, APRIL 24, 1996.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. RICHARD D. KLAUSNER, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

DR. ALAN RABSON, M.D., DEPUTY DIRECTOR

DR. HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION OF WITNESSES

Mr. PORTER. The subcommittee will come to order.

Our hearings continue on the National Institutes of Health today with the National Cancer Institute. And we're pleased to welcome Dr. Richard Klausner, the Director. Dr. Klausner, it's good to see you. And Dr. Varmus, Mr. Williams. And why don't you introduce the gentleman on your left?

Dr. KLAUSNER. Dr. Alan Rabson, who is the Deputy Director of the NCI.

Mr. PORTER. Please proceed.

OPENING STATEMENT

Dr. KLAUSNER. Thank you very much, Mr. Chairman, and members of the subcommittee. I'm honored to be here before you for the first time as Director of the National Cancer Institute. The NCI represents this Nation's investment in hope that we can and must reduce the burden of cancer.

We're all frustrated by this disease and by the difficult challenge its eradication has proven to be. We all know the statistics: greater than 40 percent of us in this country at some time in our lives will be diagnosed as having cancer, and about half of those who are diagnosed will die from the disease, if we do not better learn to prevent and to treat it.

As a scientist trained to cast a skeptical and questioning eye on promises and predictions, I can honestly report a growing but cautious optimism that we are indeed finally learning what causes cancer so that we can prevent it. And more importantly, we are finally truly figuring out what cancer is. And that knowledge, which has exploded over the last few years, will, without any doubt, determine our eventual ability to better detect, to diagnose and to cure the disease.

We have made some progress. We know the preventable cause of the number one cancer killer, lung cancer, and that's smoking. And after enormous effort, the rates of smoking in all segments of our population except the most vulnerable to addiction, that is adoles-

cents, have dropped. And the peak incidence of lung cancer in men has already been seen and is being reduced.

MORTALITY RATES

Subtracting this preventable cause of cancer death, mortality rates for cancer in fact have dropped. Cancer survival is possible. Cancer is not necessarily a death sentence. We can see in this chart what has happened to the five year survival from all cancers in our population.

In the red curve, we see the dramatic triumph of our ability to treat, and indeed to cure, the majority of our children who are diagnosed with cancer. We can see in the blue line all adults, and we can see this increase, so that now almost 60 percent of individuals diagnosed with cancer survive for five years. Also shown in this line is the unacceptable lag in our country of the survival rates for African-Americans.

We can treat cancer, we can diagnose it early. Currently, because of that, in this country, there are greater than 10 million cancer survivors. The majority of them have been diagnosed more than five years, and many of those can in fact be presumed to be cured. Survivorship is becoming an issue for us.

We now need to look at research questions beyond the acute diagnosis and treatment, beyond prevention, and deal with the many research issues that are presented by individuals who are survivors of cancer. We are setting up a new office at the NCI headed by Anna Meadows, an expert in this area, to deal with the need to develop a research agenda for survivorship.

The ability to cure cancers is not limited to the occasional rare cancer. There are some cancers now that we can predictably cure. In others, the most common, unfortunately we can cure some patients and not cure others. We don't know why, and I'll come back to that.

There are encouraging changes in the mortality rates for even some of the most common and devastating cancers. I want to show you some recent data, which is the mortality rate from breast cancer. What we can see in three different countries, the United States, Canada and the United Kingdom, starting at about 1990, is a significant and what may perhaps prove to be a dramatic downturn in the last few years of a 7 to 10 percent drop in mortality, and looking at the latest figures we have from 1993, it continues to drop.

CANCER DETECTION

For the first time, we are beginning to see in this country a leveling off, and in younger women, a drop in mortality in African-American women in this country. We see drops in the mortality also for other common cancers; colon cancer in some groups has dropped by 20 percent, due primarily to early detection and better treatment, even for locally advanced colon cancer.

The same thing is true for other common cancers, such as bladder and head and neck cancer. We need to deal with the ability to create better and more reliable screening methods. We know that many of the cancers that are now incurable can be cured if they're caught early. For some cancers, we have screening methods, for

some we don't. For all cancers, screening methods have to get better.

We know that mammography can save lives. The NCI will be looking in the next few months at new data from five Swedish studies suggesting that there will be evidence that screening women below the age of 50 can reduce mortality. We will be looking at that data and analyzing it soon.

We cannot stop with our current detection technologies. And we are moving ahead to develop new detection technologies for many cancers. Breast cancer is one of them. I show here an example of a young woman from a family with a high incidence of cancer, a 34 year old woman who had a normal mammogram. We, in partnership with industry, as well as other government agencies, such as the National Aeronautics and Space Administration, the Department of Defense and the CIA, are examining new methodologies for the detection and analysis of detection of breast cancer.

In this example, we see the same woman's breast using a technique called MRI. And while this mammogram was read as normal, we see that this woman in fact had multiple breast cancers. We need to and we will do better with the development of detection technologies.

We know that detection technologies for colon cancer, the second most common cause of cancer death in the United States, can lower mortality. We are developing new techniques to replace, hopefully, invasive colonoscopy with what we're referring to as virtual colonoscopy, which is done with external imaging.

CANCER GENETICS

Several million individuals in this country are born with a genetic predisposition to cancer. Their genetic script puts them at extremely high risk, some of them as high as 90 percent, to develop cancer at some point during their life. This is not a minor problem. As I said, there are several million Americans with such inherited predispositions. What does it mean? Why is it that we spend so much time and talk so much about the identification of cancer predisposition genes?

Let me just illustrate what it means with a gene that my own laboratory is working on, a gene that was discovered at the clinical center of the NIH for a relatively rare disease called Von Hippel-Lindau disease, described about 100 years ago. This is a familial syndrome, where individuals develop cancers of the kidney, of the brain, tumors of the eye and of the adrenal glands. Individuals in these families have a very high incidence of these tumors.

I want to explain how the identification of the gene has already dramatically and beneficially affected clinical practice. We at the clinical center saw a 19 year old girl from this family, because she had a rare adrenal tumor. We suspected that she had Von Hippel-Lindau, or VHL, due to an alternation in a gene that was cloned two years ago at the NCI. Before then, we didn't know what it was.

We identified that this young woman in fact carried and had inherited an altered gene, and identified that it was inherited from her father, who at the time was perfectly well. By careful medical testing, we discovered that her father had early kidney cancer and

early adrenal cancer, cancers that in fact can be cured when they're caught early, and they were caught early.

As importantly, we found that her sister had a tumor of the eye that was threatening her vision. These individuals can go blind, and they often do. However, it is completely curable with laser photocoagulation therapy, and that's what she received, and she is now fine.

Her 12 year old brother, a very healthy football player, was discovered only by intensive surveillance to have a small adrenal cancer, again, which was removed, and he's back playing sports. We've been able to tell the family that their other child did not inherit the gene.

There are enormous problems, enormous challenges for us as a society, as a scientific and as a medical organization, that knowledge about genetic predisposition brings. We must address those issues. The NCI has proposed to create a new national cancer genetics network to allow the country to deal with the many issues; medical, scientific, and counseling, that we will need to deal with as medicine is transformed by this new information.

Let me tell you something else about this gene. This gene is not simply altered in these rare inherited syndromes. Soon after discovery, we found out that the vast majority, if not all of the 30,000 new cases of kidney cancer in this country a year are the result of the acquired abnormality of the same gene. That gives us the opportunity for the first time to think about, which we are looking at, the development of a urine test to detect kidney cancer, again, a cancer that we have no therapy for unless we catch it early.

So the identification of these genes provides us with unparalleled windows into the nature of all cancer. And that brings me back to this question about why can we cure some individuals and not cure others. We know that all cancers, regardless of their proximal cause, be it environmental carcinogens or endogenous carcinogens, or simply mistakes in copying DNA, are the results of changes in genes.

The pattern of those genes represents the predictor of the behavior of that cancer. Will it grow, will it grow fast, will it spread, will it metastasize, will it respond to therapy and what therapy? We are switching from using the microscope to identify and diagnose cancer, to utilizing the signature of genes that have been changed, that actually tell us what the cancer is. Let me give you an example.

One of the most common cancers in children is neural blastoma. About 60 percent of these children can be cured. But why 60 percent? To the pathologist, all of these neural blastomas look the same. So we treated them the same. But a fraction of them have a particular genetic abnormality that has been acquired, not inherited. And a fraction of them don't.

You can see on this chart the fraction that don't have one of the particular genes that we can look for. Eighty percent of them can be cured, and they can be cured with relatively mild, non-toxic therapy. We don't have to subject these children to life threatening therapy in order to try to cure them. We now know that new and more profound therapies have to be directed at this new group.

And this is going to give a flavor for how we're going to be dealing with all cancers. We know that some individuals with breast cancer respond to therapy, some don't. We need to know why to address this new world of cancer. It's a new world taking place in a very changing landscape of medicine and science. When I became the Director of the NCI, I recognized that it was time and there was a need for fundamental changes in the structure and the processes at the NCI. We have moved quickly, we have moved dramatically to make significant changes in the institution.

NCI REORGANIZATION

We have undertaken, I believe, the largest single reorganization in the history of the agency, a reorganization aimed to realign the institution to the scientific needs and the scientific opportunities, a reorganization aimed at making sure that every aspect of the institution, how it functions, is addressed to advancing science.

And so, for example, we have restructured the administration so that it is easier, more facile, less bureaucratic, quicker, and we save money. We need less positions. This chart is just an example of the previous way that we made decisions to agree about purchasing or hiring. And this is the new, simplified structure. It is a structure that is working, and it's working well.

We're now saving approximately 40 percent, for example, on the cost of developing contracts. Everything is happening more quickly and we will need fewer administrative positions to run the Institute.

More important is that we've made fundamental changes in the way we make decisions, the way we plan. And part of those fundamental changes is to open the institution up to bring in the external community, that is all of the communities that have a stake in cancer, to advise us, to be part of our decision making process, to advise us on where we're going.

For example, I have commissioned groups that are going to tell us what cancer centers, clinical trials programs, prevention research, controlled research and developmental therapeutics should look like. We have established working groups in order to deal with this post genome world that I mentioned. In fact, it is being chaired by Dr. Arnie Levine, who just wrote the OAR report on AIDS research. He is now part time at the NCI. We're trying to corral as many of our colleagues as possible to help us in this task. We have a working group on AIDS malignancy, a working group on cancer genetics, and a working group on preclinical models.

And finally, we've moved to address the critical issue of how is it that we're going to make sure that these marvelous and surprising advances in the laboratory accrue to the benefits of patients, accrue to the benefits of populations at risk. We need to address the threats and the barriers to patient-oriented research.

We have done that in a variety of ways. We've created a new, experimental approach to our grant system for individuals that do patient-oriented research. We have come to grips with, or at least begun to come to grips with, the need to negotiate with payors and providers, so that they will participate as partners with the NIH in assuming the clinical costs for individuals to participate in clinical trials.

And as you know, we recently completed an agreement with the Department of Defense to allow their 8.3 million member system to be truly integrated into the nationally disseminated NCI system for clinical trials for all phase two and phase three clinical trials for cancer.

In addition, we have put new monies, new monies that were received because of the generosity of the Congress, into the clinical cooperative group system, particularly to do translational research. We also have begun a new initiative to take the entire national cancer program, including our clinical research program in epidemiology, in tissue and tumor banks, in DNA banks, in clinical trials and cancer centers, and to link them together in a modern informatics system.

We have been busy. A lot has happened. A lot has changed. The atmosphere, as Dr. Varmus pointed out, is one of optimism. The President is requesting for the cancer program a budget of \$2,060,392,000 for fiscal year 1997. I will be more than happy to answer any questions that you have about the National Cancer Institute.

[The prepared statement of Dr. Richard Klausner follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Statement of the Director

I am here today to talk about progress and how to build on that progress. We measure progress against cancer by gains in two broad areas: the growth of knowledge about cancer and the decrease in the burdens imposed by cancer. Knowledge about cancer has grown enormously in the past few decades and its pace continues at an astonishing rate. We now know that cancer has a genetic basis. We have learned of specific genes that either promote or inhibit tumor growth and each year brings the discovery of more such genes. We used to theorize that chemical and physical damage and viruses caused cancer. Now we have hard evidence that they contribute to cancer because they lead to altered genes and gene function.

Ideas abound on how to use our new and ever increasing knowledge of cancer genes, and there is no doubt that this knowledge is opening new avenues in cancer prevention, diagnosis, and treatment. Progress in each of these areas can reduce the burden of cancer on individuals. This is the second way we measure progress against cancer and it is the ultimate aim of the National Cancer Institute.

A decreasing burden is evident already for several cancers. Deaths from children's cancers have declined by more than 50 percent over the past 25 years. Breast cancer mortality has begun to decline, down 5 percent since 1989 thanks to advances in chemotherapy, hormonal treatments, and access to and use of screening mammography. Deaths from colon and rectal cancers, Hodgkin's disease, and testicular cancer have dropped due to better therapies and lung cancer deaths for men have declined after a intensive, sustained anti-smoking campaign.

But death from lung cancer is rising among women, one sign of the formidable challenges still ahead. Cancer incidence overall is rising and among some ethnic and racial populations, the risk is disproportionately high. We will reach our goal of reducing the cancer burden only by translating our burgeoning knowledge of cancer into strategies that will benefit all people who are at risk for and have cancer.

Both increasing knowledge of cancer and reducing the burden of cancer have their base in three fundamental areas of cancer research: cancer biology, cancer risk, and cancer interventions. The most remarkable progress in the last 25 years has been in our knowledge of cancer biology. Not only have we begun to identify what genes, when altered, cause a normal cell turn into a cancer cell, but we are also now learning how those genes cause cancer. Researchers recently have identified genes -- BRCA1 and BRCA2 -- that are responsible for breast and ovarian cancer in some families. Now we are building on that breakthrough, asking new questions: What roles do these genes play in normal breast and ovary cells? How does an alteration in the genes change that role? And how do the altered genes interact with hormonal and environmental factors to

influence which cancers will develop and when?

We are also beginning to understand the evolution of cancer. We know that it takes more than one genetic alteration to turn a normal cell into a cancer cell. In fact, it takes an accumulation of changes during the lifetime of a cell, and this understanding allows us to begin to define stages in the development of cancer from predisposition to precancer to cancer. New advances in our ability to detect, diagnose, and treat cancer are now growing from this understanding of the evolutionary patterns of specific cancers. For example, we are learning about the molecular markers that characterize the earliest stages of lung, bladder, and cervical cancer, among others, and devising tests to detect those markers.

The second fundamental area of cancer research is the study of cancer risk, which quantifies the risk of developing cancer in various populations and individual and looks for the factors that raise or lower risk. By investigating risk, epidemiologists have uncovered distinct cancer patterns among various population groups. For example women in Asian countries have the lowest rates of breast cancer in the world while those in western countries have the highest. But when Asian women migrate to the United States, their breast cancer risk rises over several generations until it matches that found in white women in the U.S. Findings like this one offer clues to lifestyle or environmental risk factors and help us in targeting further research into the causes of cancer.

Studies of cancer risk taught us about the link between cancer and tobacco, diet, alcohol consumption, x-rays and ultraviolet light, exposure to asbestos and other occupational risks, environmental pollution, some pharmaceutical agents, certain viruses, and hormonal factors. From our studies of risk come NCI's ongoing campaigns to prevent smoking, particularly among young people, and to provide other information people need to reduce their risk of cancer.

The study of cancer biology and the study of cancer risk both have a common ultimate aim: the development of interventions. Better interventions -- that is, more effective ways to prevent, diagnose, and treat cancers -- are at the center of NCI's mission.

In this area, major challenges lie ahead. But critical advances in the past 25 years give grounds for optimism. For example, a better understanding of normal immune system development and biology has led directly to molecular techniques for classifying, for the first time, immune system tumors called lymphomas. Such advances are critically important because they lead to more precise predictions of clinical outcome for patients and to the discovery of more effective therapies. We expect that similar biological advances will revolutionize tumor diagnosis and classification in the coming years.

As we work toward better interventions, we are developing highly sophisticated tools for finding cancers at a very early stage. Computed tomography, magnetic resonance imaging, and ultrasonography did not exist as useful clinical tools 25 years ago. Now, they not only let us locate tumors with unprecedented accuracy but also to biopsy internal organs without the need

for major surgical procedures. In fact, invasive procedures, such as colonoscopy and bronchoscopy are on the verge of giving way to "virtual" procedures, which give images of these internal structures without any actual invasion of the body by tubes or scopes. As we build on progress in this area, we are interested in integrating electronic and computational capabilities to manipulate images. For example, the application of neural networks to patterns visualized in standard X-ray mammography has already suggested that neural networks can be "taught" to distinguish between malignant and non-malignant breast images with impressive accuracy. Since we already know that mammography saves lives, we are excited about the further development of this technology.

Cancer prevention strategies are another kind of intervention. There are a whole class of interventions that fall under the heading of chemoprevention -- drugs or other agents that may prevent cancer. The testing of tamoxifen to prevent breast cancer in women at high risk is one example. Another is 13-cis-retinoic acid, which we have learned is effective in preventing oral cancer. The large clinical trials of beta-carotene supplements have shown they do not prevent lung cancer and given us the information needed to move forward with other hypotheses about the link between diet and cancer. More work and progress in chemoprevention lie ahead, although major improvements in this area will depend on a better understanding of the fundamental mechanisms by which normal cells become malignant.

The past quarter century has seen major progress in our ability to treat certain cancers. Adding chemotherapy to surgery and/or radiation has increased the cure rates for patients with breast and colorectal cancer. High-dose chemotherapy with stem-cell rescue is effective in leukemia and is now undergoing definitive testing in advanced breast cancer. Moreover, molecular biology has brought significant advances in the drug discovery process by permitting the large-scale production of proteins by recombinant DNA technology. The availability of interferon-alpha, for example, has improved the outlook for people with one form of leukemia and both interferon and interleukin-2 are effective for some patients with kidney cancer. Several interleukins show promise against AIDS-related cancers, such as Kaposi's sarcoma. Other novel therapies involving vaccines against cancer have moved from the laboratory to clinical trials, where they show promise against melanoma, metastatic breast cancer, and colon cancer.

NCI is also committed to finding interventions that will improve the quality of life for people with cancer. Over the past 15 years, we have developed drugs that help block the formidable problem of nausea and vomiting that often accompanies cancer treatment. And we are also developing techniques that avoid some of the most acute side effects of treatment. For example, one landmark clinical trial showed that chemotherapy followed by radiation treatment is as effective as total removal of the voice box in treating cancer of the larynx. This finding has made it possible for many survivors of this form of cancer to retain natural speech. We are committed to continued progress in quality-of-life research, including psychosocial and behavioral research. In fact, as we learn more about the genes that place people at risk for cancer, difficult prevention and treatment choices will arise, making psychosocial research ever more critical.

Finally a word about cancer control. The final step in carrying out the basic mission of the NCI, cancer control includes research to find effective ways to apply information flowing from more fundamental research efforts. Research in the other three areas -- biology, cancer risk, and interventions -- all provide a foundation for cancer control. Ultimately cancer control involves behavioral changes on the part of both health professionals and individual Americans, so the communication of research results plays a central role. The NCI maintains several important lines of communication, including its nationwide Cancer Information Service and its Physician Data Query information system. Its scientific publication, the Journal of the National Cancer Institute, has one of the highest citation rates of any medical journal.

To facilitate and accelerate progress in all three areas -- biology, cancer risk, and interventions -- we initiated a major reorganization at NCI in the past year. We re-grouped our extramural programs and consolidated intramural research under three new divisions. We have reduced overlap and duplication, instituted cost efficiencies, streamlined program management, and realigned NCI's structure with current scientific priorities. Zero-based budgeting and the decentralization of authority have enhanced scientific program management and streamlined administration. These organizational changes should improve communication between scientists working in related areas and foster a uniform standard of intramural research excellence. And by revamping our advisory committee structure, the reorganization has achieved stronger participation in decision-making by the cancer research community.

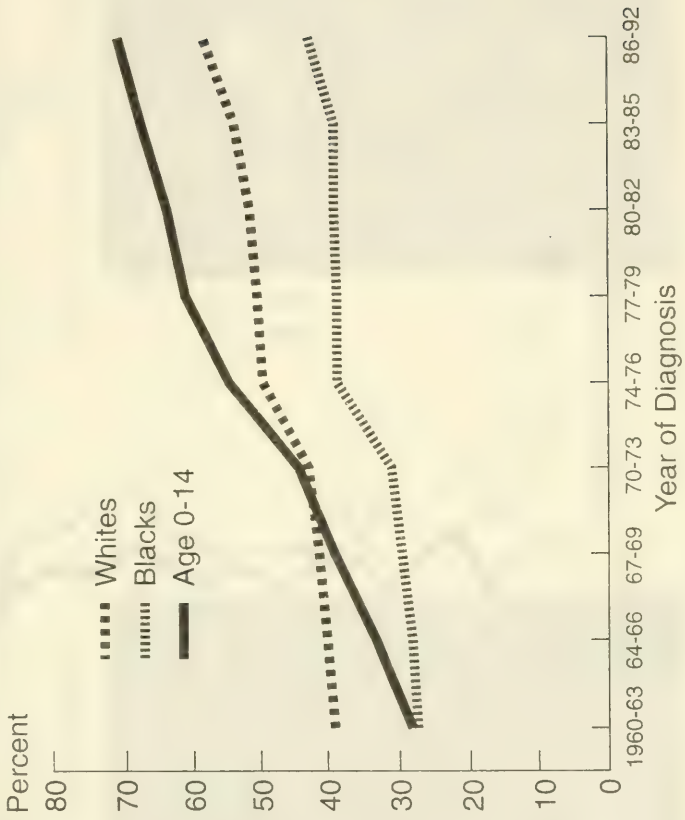
The budget request for 1997 is set out under eight major categories, which represent the infrastructure that supports progress in cancer research. This infrastructure includes individual researchers in hundreds of institutions across the country, the intramural research program, cancer centers and clinical trials, training and education, cancer control, AIDS research, and research and management support.

Within this infrastructure, funding decisions are based on two main factors. First is the advice of scientists themselves as to the areas and projects that have the greatest potential to expand our knowledge of cancer. The most important component of our research program is investigator-initiated research. The second critical factor in our funding strategy is the burden of specific cancers. Thus cancers that affect large numbers of people, such as breast and prostate cancers, are priorities.

Keep in mind, though, that no research allocation plan can account for the essential inter-relationships between cancers or trace all the lines that link fundamental and applied research. Research on testicular cancer, which occurs in about 7,000 people annually, could illuminate some hormonal aspects of prostate and breast cancer, which occur in hundreds of thousands of people annually. Progress against one kind of cancer will further our understanding of other kinds. And these advances come from both targeted research and, more often, nontargeted research which has the potential to apply the engine of discovery to all cancers.

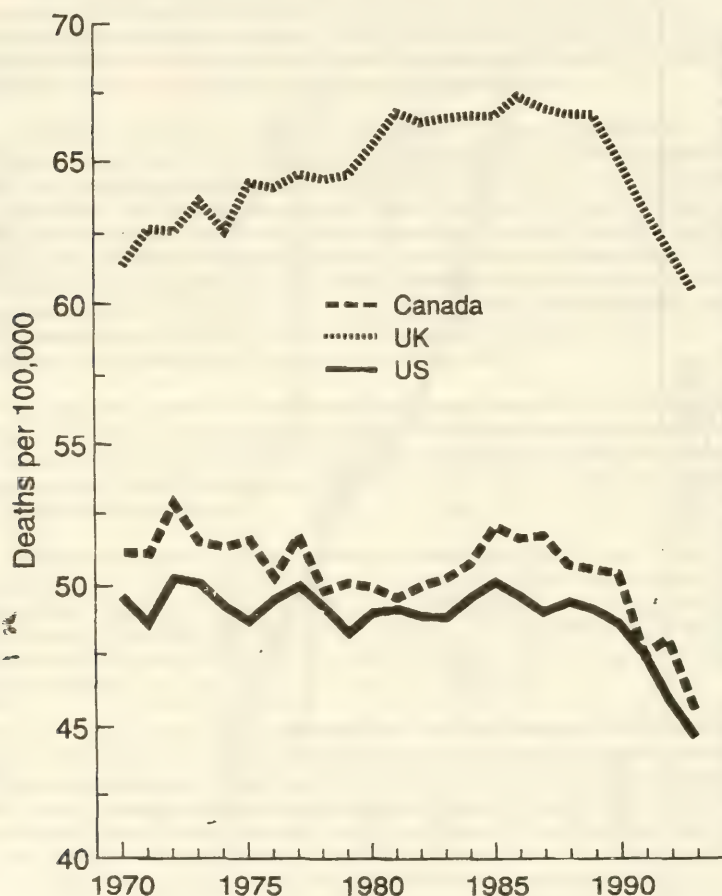
Mr. Chairman, the budget request for the National Cancer Institute for FY 1997 totals \$2,060,392,000. I will be please to answer any questions. Thank you.

5-Year Relative Survival Rates (All Sites)



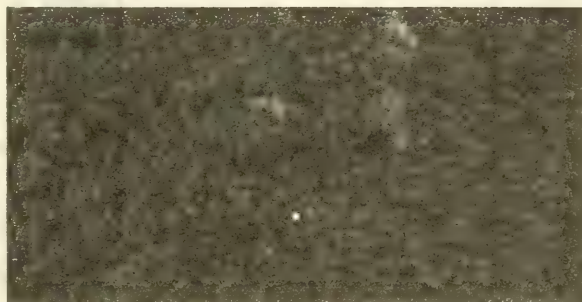
Breast Cancer Mortality

Age-Adjusted Rates for 30-74 Year Olds

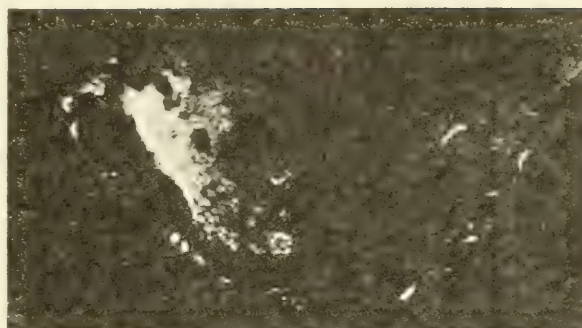


Breast Cancer Imaging Technologies

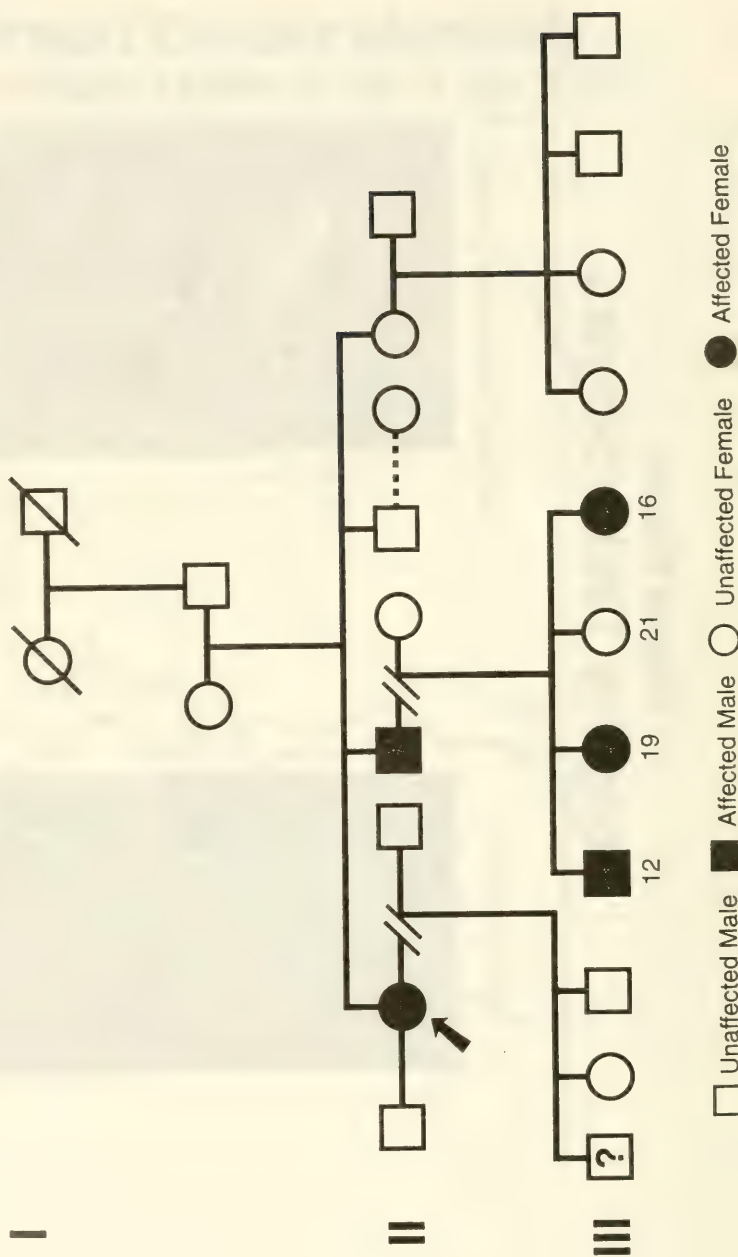
Mammography



Magnetic Resonance Imaging (MRI)



Von Hippel-Lindau Syndrome A Family Tree

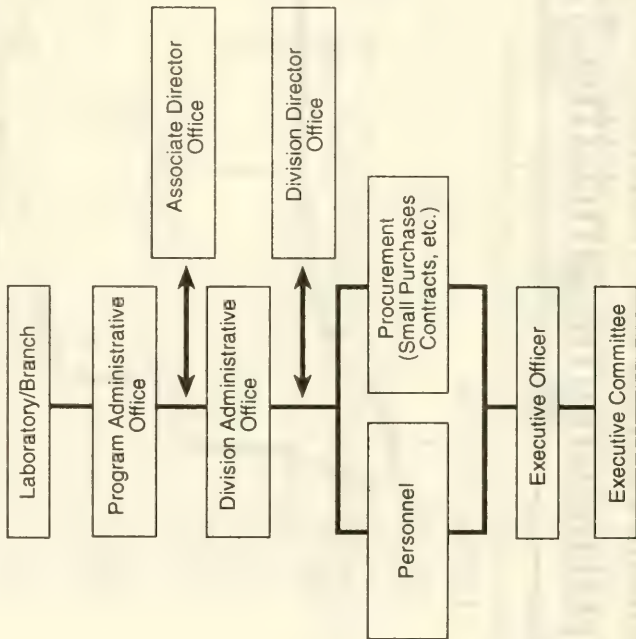


Genetic Factors as Predictors of Treatment Outcome Neuroblastoma and the 1p Chromosome

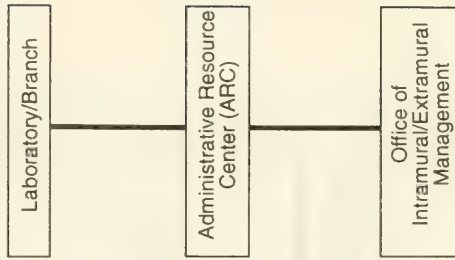


Administrative Processing

Previous



Current



Mr. PORTER. Dr. Klausner, I had not remembered that this is the first time that you've testified before the committee, I think probably because you and I have talked so many times. And it's really too bad that you don't bring any enthusiasm to this job. [Laughter.]

GRANT PAYLINES

I have never seen anyone go at a position the way you have, and bringing a vitality and a new way of looking at things and restructuring and doing the things that I believe we have to do all across government in every single agency, and look afresh at the way we conduct the government's business, and see if we can do it better.

And you've certainly been a real example of reinventing government. I don't like the term reinventing, but reinventing government is what's happening here. And I commend you for the real strength and vitality you've brought to this position.

You also answered my first question about your reorganization, although any additional detail you'd like to share with us on the changes that you've made, we'd be happy to hear.

But I was interested to learn about your recent actions to reallocate up to \$40 million from other mechanisms to research project grants, resulting in a projected increase in the Institute's pay line from the 15th to 23rd percentile. Which other mechanisms did you cut, and why did you feel they could absorb a reduction?

Dr. KLAUSNER. We recognized that the heart of the Institute is investigator-initiated research, as Dr. Varmus has been talking about. We needed to make sure that we had looked at every nook and cranny to make sure that we were spending the money that we had, our precious resources, in the way that we wanted to.

So I chaired a group that looked at every line. The two areas that we looked at most particularly were the intramural program, and contracts. The intramural program has been restructured; for the first time we've introduced zero based budgeting and cost management principles. We were able to save a significant amount of money there. I can come back to that later.

But also, we looked very hard at the large contract line; some of these contracts had not been carefully looked at for some time. We looked at them one by one. Every one had to be presented to me. And we asked the question, did we still need them, were they producing, were they producing at 100 percent or 90 percent or 80 percent. And from the contract line alone, we were able to free up over \$30 million. We put that into the Research Grants pool, knowing that that is the primary pool that is going to drive progress in cancer.

RPG REVIEW PROCEDURES

Mr. PORTER. Another one of your innovations is an accelerated review of research applications within a few points of the pay line cutoff, so that researchers, especially clinical researchers, don't become discouraged and disappear from the applicant pool. I would ask you and perhaps Dr. Varmus as well, does this concept have applicability campus wide as a way to encourage clinical research?

Dr. KLAUSNER. It's a program that we're watching work, and it's working incredibly well. We all recognize that one of the most destabilizing aspects of the funding process is to get close to funding,

but not get it. And you have to go back into a queue and wait and sometimes the funding takes eight months or a year or a year and a half. Especially for patient-oriented research, that can be a disaster.

So what we did is we set aside funds and we told the individuals that for patient-oriented research, if they were within 10 percentile points of the pay line, up to the 33rd percentile, that we will send them the peer review critiques, which are very important, and they, as quickly as possible, should write me a letter, no more than five pages, of what they are doing scientifically to correctly address those problems.

Then I and my executive committee every week review those grants. And every week we make decisions about whether they have correctly and successfully responded to the peer review. About 50 percent of them do. We call them immediately and they can begin their research. I think it's a process that's working fabulously.

Dr. VARMUS. If I could just respond to that, Mr. Porter. We have given general advice through Dr. Wendy Baldwin's office, the Office of Extramural Research, to the institutes to consider a very similar kind of mechanisms. We know from experience that individuals who are within a few points of the pay line have a very high chance of receiving a fundable score in the next round of review, which takes nine months to go through.

So we're encouraging institutes to take any one of several courses. If it is a competing renewal, one is to give what might be called a "bridge grant"; we talked about this last Thursday. The other would be to do what Dr. Klausner has decided to do, to have a quick review. And the important thing, of course, is that there be some means in the Institute to review the responses to the critique. Because what we don't want to do is swear off peer review of that response. That's a very important element.

CANCER SITES

Mr. PORTER. Dr. Klausner, you've spoken of shifting the Institute's orientation from an organ emphasis, such as breast cancer or lung cancer, to focus on the disease process of cancer. The advocacy groups tend to be organized around site specific cancers. Is that also true for the research community or will they be able to shift gears?

Dr. KLAUSNER. Well, I think the research community has long recognized that it is very difficult, often impossible, to know what cancer you're working on. That's not entirely true. We obviously need a balance. But it is clear that most of what we are learning that is going to affect breast cancer, prostate cancer, colon cancer, lung cancer, will be fundamental to the nature of cancer itself. And we need to make sure that we maintain lines of communication across special interests so that we recognize that we're actually all working towards the same goals.

An important aspect of that is for the Institute to be open to and to work very closely with the advocacy groups, which I've tried to do. We set up a new liaison office to make sure that there is good communication, so that we actually can both be looking at the needs that are specific for different cancer sites, as well as the sci-

entific opportunities either associated with those sites or associated with the general problem of understanding cancer.

DIAGNOSING AND TREATING PROSTATE CANCER

Mr. PORTER. Mrs. Lowey.

Mrs. LOWEY. Thank you very much, Mr. Chairman.

I just want to make it clear that I share the enthusiasm of our distinguished chairman for your enthusiastic and innovative leadership. And we really appreciate the work you're doing.

And just so this committee doesn't think that I have a parochial interest in breast cancer research, I want you all to know that I care very much about the gentlemen in my district, and I would like you to share with us the change in the incidence of prostate cancer in recent years. Can you discuss the process that NCI is making with regard to diagnosing and treating prostate cancer? The numbers I think are now one in five.

Dr. KLAUSNER. Yes. About 18 percent of men will be diagnosed with prostate cancer over the course of their lifetime. And the incidence has skyrocketed. We believe that much of that skyrocketing incidence is due to the use of Prostate Specific Antigen testing. I have just looked at the latest data about incidence and between 1992 and 1993; now for the first time, the incidence of prostate cancer in white males will drop by 14 percent.

The incidence of newly diagnosed prostate cancer in African-American males had gone up between 1991 and 1992 by something like 11 to 15 percent. And this year, for 1992 to 1993, which are the latest numbers, that dropped, to an increase of 4 percent. What this suggests is that we are saturating or beginning to saturate the use of the PSA screening approach.

Now, mortality rates are also continuing to go up. And so that can't just be a problem of screening. We don't understand that. We have many programs and many projects looking at incidence, the environment, issues of environmental causes, and hormonal causes.

One of the most important issues, in prostate cancer that we're looking at, is the value of screening. Does PSA screening and other screening in fact reduce mortality? And we need to understand this very puzzling disease. Because perhaps more than any other cancer, many, if not most, prostate cancers, are extremely slow growing. They are diagnosed in older individuals.

What we need to be able to do, is contained within that molecular signature of what a cancer cell is. We need to be able to predict those prostate cancers that we can just watch and those prostate cancers that will progress and that we will have to treat. And we are doing a large number of studies throughout the country to try to address both the screening issues as well as the trying to predict the characteristics of prostate cancer, to determine whether they need to be treated or not.

Mrs. LOWEY. Incidentally, this question is probably a question for Dr. Kessler at the Food Drug Administration, but in recent weeks, we've received, I guess my husband has received, information in the mail from a doctor in Canada on all kinds of mixtures that would prevent prostate cancer, if you took it every day.

I would be interested in pursuing this. I don't know if you are involved or aware of a lot of these, I don't want to say placebos. They may be very good. Are you aware of a lot of these circulars that are being sent in the mail?

Dr. KLAUSNER. I'm not aware specifically of them.

MAMMOGRAPHY SCREENING

Mrs. LOWEY. A question about mammography screening. I understand that there is new Swedish data regarding the age at which women should be screened regularly for breast cancer. Can you comment on these new findings? Are they controversial and what is NCI doing as follow up?

Dr. KLAUSNER. Yes. There was a meeting in Sweden which reviewed five different Swedish trials where mammography screening begins at the age of 40. The results reported at those meetings are that mortality rate in that population of women dropped by about 23 percent. And it was statistically significant.

We are very interested, of course, in that data. We sent representatives there. I have invited all of these investigators to submit their data for publication in the Journal of the National Cancer Institute, and we are now organizing a meeting to be held as soon as possible, sponsored by the NCI as a new consensus conference, where we can view those data.

While we are very excited and encouraged about those reports, those data have not yet been analyzed and subject to the scrutiny of peer review. But we are all very interested, very excited, and our suspicion is, I must say, is that the data looks very good.

Mrs. LOWEY. We've been hearing for several years that mammography is far from perfect for finding breast cancer. Are there new technologies being developed by NCI, and are there any technologies that show some promise?

Dr. KLAUSNER. Yes, there are. First of all, mammography itself can be improved in many ways. We are developing digital mammography, which is still early in development. Real advances are being made primarily in image analysis using technologies that were largely developed, in the defense industry.

In addition, we are particularly interested in the encouraging results I showed before you came in of breast MRI, which, in this example is capable of reading and seeing cancerous lesions even when, from that same woman, the mammogram is read as absolutely normal. And in fact, this year we will be instituting a large scale clinical trial in breast mammography. This has been developed because of consortium between the NCI and industry to develop breast mammograms.

There are other imaging technologies that will help, including something that Dr. Varmus mentioned, and that is the ultrasonography, which allows one to look at small breast lesions, and quite successfully predict which will be benign and which will not be benign. We hope that this will save a large number of unnecessary biopsies.

Mrs. LOWEY. I gather my time is up. I just want to say, because I didn't say it in my introduction, that I'm not surprised at the great talent of Dr. Klausner, because he grew up in Yonkers, New

York, which is in my district. And we are delighted to have you here in this position. I'll save the questions for the next round.

Mr. PORTER. We will have as many rounds as we need to.

POLITICS AND SCIENCE

Mr. Wicker.

Mr. WICKER. Thank you, Mr. Chairman.

And I, too, welcome Dr. Klausner to the hearing. Let me just ask you about a little controversy that has come to my attention in the last few weeks. Could you describe the work of Dr. Stanton Glantz, the voting analysis of how tobacco campaign money influences state legislators, particularly, how much did the Institute spend on this?

The subcommittee has tried to get politics out of science and let the scientists practice scientific research. Do you believe that this brings the scientists into the area of politics, and do you think this is an appropriate expenditure of your funds?

Dr. KLAUSNER. Well. Dr. Glantz, who is a professor at University of California at San Francisco, really has made enormous contributions to our understanding of the role of tobacco in cancer and specifically, the behavioral issues that lead individuals to become addicted. The specific issue in the grant that you're referring to is an area of that grant that we are no longer funding.

And based upon the recommendations of this committee last year, all of the aspects that relate to voting records of state legislatures has been separated out from Dr. Glantz' grant. There was only a small part of a larger grant looking at patterns of tobacco use and the relationship to advertising. And the NCI is no longer funding that.

Mr. WICKER. Can you estimate how much of the funding went to that particular aspect?

Dr. KLAUSNER. We are now doing an accounting. Our best estimate was that about \$74,000 of a much larger grant was aimed at that particular piece of the program. And that is, as I said, is no longer being funded.

Mr. WICKER. I have an article from the Los Angeles Times dated April 14 of this year, which says that the Cancer Institute opened negotiations with Congress to lower the price tag of the grant, but to let the work continue.

Are you saying that the other aspects of Dr. Glantz' research will continue?

Dr. KLAUSNER. Yes. The other aspect of Dr. Glantz' research will continue. We think it's been valuable. In peer review, it has always gotten the highest ratings and we think it is really very contributory.

We recognize that there is a very difficult boundary issue of when science becomes political science. And the best we can do is to use our best judgment to continue to look at all that we do that deals with issues that come up to those sorts of borders. But the rest of Dr. Glantz' grant was looked at very carefully and was deemed not to be an area that we should not be committed to, and it will continue to be funded.

Mr. WICKER. Possibly someone should be doing such a study, some public interest group, maybe the American Cancer Society. I think the Chairman can speak for himself, but apparently there's

been some communication that suggested that that's not the purview of the Federal science agency.

GENETIC LINKS TO BEHAVIORS LEADING TO HEALTH PROBLEMS

Let me ask you about another study, reporting on a collaborative study which was recently completed, establishing a genetic link to behavioral activities, such as susceptibility to HIV from homosexuality and tobacco abuse. Is it your conclusion that some people are born with a gene which makes them more susceptible to high risk behavior?

Dr. KLAUSNER. Well, I certainly do not make a conclusion, and that's why the research is going on. There is an intense interest to try to understand whether there are genetic components to complex behavior. It is clear that behavior is much more than genetics.

But we do need to ask questions about what genetic components are to the likelihood of becoming addicted, for example, and addictive behavior. And there is a new field of genetics developing which uses a technique called quantitative trait analysis.

This is an area that is going to be extremely important, whether it's cancer susceptibility, susceptibility to carcinogens. Why do the 10 percent of people that smoke develop cancer and not 100 percent? These are all going to be due to very complex interactions between multiple genes and the environment. This will be true for behavior. It will be true for almost all aspects within the purview of medicine.

So I don't conclude anything. Because we're just at the beginning of learning how to answer those questions. And in my mind, there's no question that as we approach any aspect of genetic research, we must be very, very careful, very aware of, and cognizant of, the dangers of misinterpretation of genetics to get into an issue to assume that all is genetics. It is not. It is much more complicated. But it is an issue that we will only learn about if we study.

Mr. WICKER. I just wonder what the logical conclusion would be if we do get to the point that we determine that some high risk behavior is more likely in people with certain genes. I just wonder where we're going from there.

Dr. KLAUSNER. Well, of course, I'm not an expert in this area, but one possibility is if you identify individuals that are at particular risk for becoming addicted to alcohol or addicted to tobacco, I think those individuals may be individuals that would most benefit from interventions, counseling, behavioral interventions, etc.

And I think that's really the hope. Basically it is very difficult to change behavior, whether you choose to go to a doctor or whether you choose to listen to the doctor, it's very difficult. And we need to be able to understand which individuals need most of our attention.

Mr. PORTER. Thank you, Mr. Wicker.

NEW MANAGEMENT APPROACHES

Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman.

Welcome, Dr. Klausner, welcome again, Dr. Varmus. I am again in two places at once. Fortunately, this time my other committee is right next door, Mr. Chairman—your other committee, too, For-

eign Ops. So I'm sorry I could not hear Dr. Klausner's presentation. But I did have the opportunity to review his testimony and the budget proposal.

And Dr. Klausner, congratulations to you for your excellent work at the NCI, and particularly, I wish to commend you on the NCI bypass budget and your commitment to all approaches to "all cancers in all people." It is my understanding that you've moved toward increased community consultation in planning for budget priorities for the NCI. Could you briefly tell us how this works?

Dr. KLAUSNER. Yes. One of the ways we've done that is by creating a new advisory system, which for the first time includes consumers and patient advocates.

Also, the collected recommendations that are incorporated in our planning, which is what this new bypass budget represents for the future, includes recommendations from the set of working groups that we've set up. And each of these working groups that we have, which are advising the institution on what we do, what we can do, what we can do better, include representation of all communities that we believe can, must and should participate in our process. And those include consumers, patient activists and patient advocates.

Ms. PELOSI. You indicate you have realigned NCI structure with current scientific priorities. What specific changes are reflected in your budget request?

Dr. KLAUSNER. Well, one of the things that we've done is to create a new Division of Cancer Epidemiology and Genetics, so that we are prepared to deal with the gene environment interactions that we're going to need to understand, to deal with all these challenges that we're all reading about in the newspaper all the time.

We have moved to separate structurally the intramural program from the extramural program so there's not a confusion about very different mechanisms, so that we can clearly define what we're spending intramurally and what we're spending extramurally, because the questions that we need to ask, the approaches that we need to take, are very different.

And again, as I mentioned before, I think the most important structural change is a fundamental change in our advisory structure. The governing board of the NCI is called the Executive Committee. And what we've done is we've opened that up to put seats on the Executive Committee for individuals outside the NCI. And these are individuals that chair our various advisory boards. That is to bring a tremendous breath of fresh air into those internal discussions and to make sure that we are reality testing for the decisions that we're making.

ENVIRONMENTAL CAUSES OF BREAST CANCER

Ms. PELOSI. As you know, I join with my colleague, Congresswoman Lowey and all the members of the committee in expressing concern about the incidence of breast cancer and all forms of cancer for that matter. I am also very concerned about the environmental effects on breast cancer rates.

You indicate that women in Asian countries have the lowest rate of breast cancer in the world. However, when Asian women migrate to the U.S., their risk of breast cancer rises over several genera-

tions to equal the rates of Caucasian women. What studies are in progress, particularly in collaboration with the National Institute of Environmental Health Sciences, on environmental factors as they relate to breast cancer?

Dr. KLAUSNER. We have a variety of studies to look at specifically geographic differences. Because it's geographic differences like you've just described that give us the most profound hint that environmental effects, that may include behavior, diet, sexual practices, as well as environmental issues, have a profound impact on the incidence of cancer and probably all cancer.

Some of our studies include looking at the reasons for the higher incidence of breast cancer in the northeast, and that's the northeast and mid-Atlantic study. These are involved correlative studies where we look at exposures to environmental, potential environmental carcinogens, occupational carcinogens, electromagnetic force, where we are looking at various aspects of behavior and patterns of behavior, to see if we can correlate that with increased incidence. As you know, we also are funding, with the NIEHS, the Long Island Breast Cancer Project, aimed to look at the same sorts of issues.

Ms. PELOSI. I understand that. That was initiated by our colleague, Congresswoman Lowey.

BREAST CANCER THERAPY

One area of San Francisco, the Bay View-Hunters Point area of San Francisco has been designated as having the highest incidence of breast cancer in the U.S. So we are interested in your initiatives in terms of environmental factors.

STANDARDS OF CARE

What is the current standard of care for breast cancer treatment, and what would you say are the best treatments currently available? And if you might include experimental in that as well.

Dr. KLAUSNER. Yes. The most significant changes in treatment has been the widespread use of adjuvant therapy, be it hormonal, such as tamoxifen, or standard chemotherapy, for more and more women, in different stages of breast cancer. It's clear that those approaches and the adoption of such adjuvant therapy is in part responsible for the lowering mortality and the increased survival that we're seeing in women and breast cancer.

I think some of the more interesting studies that are being done now are preoperative, neoadjuvant therapy, where what you attempt to do is to give chemotherapy before surgery. And what we're finding is that over 80 to 90 percent of women have very significant responses to this neoadjuvant therapy. It results in essentially a downstaging of the cancer, so that it is much more likely that excellent results will be obtained with less disfiguring surgery so that more and more women can use breast conserving therapy, with the expectation of a good outcome.

There are a variety of experimental therapies, such as antibody therapies, etc. Those are very early on, and while we always have hope for them, they're too early to see.

I think one of the most important and highest priority therapeutic trials that are going on by two of our cooperative groups are

the studies looking at the efficacy of intensified chemotherapy and autologous bone marrow transplantation. We need once and for all to, in a very careful, clear study, to identify whether the individuals with breast cancer who are most at risk of dying can benefit from such intensified therapy.

BREAST AND CERVICAL CANCER—NEW DIRECTIONS

Ms. PELOSI. Could you just take that to another place, and tell us what basic science advances suggest new directions for breast and cervical cancer treatments?

Dr. KLAUSNER. For cervical cancer, let me start with that, because that's somewhat different. The most important thing is the recognition that cervical cancer is a cancer that is caused by a virus, human papilloma virus. The fact that we know that and the fact that we know that only certain subgroups of that virus, primarily what are called HPB 16 and 18, may put individuals at risk for cervical cancer, gives us the possibility that for this cancer, it is possible that we will be able to come up with, and there is real progress there, with a true vaccine against this sexually transmitted virus, which would be essential for actually preventing and hopefully eventually wiping out this cancer.

Mr. PORTER. Mr. Stokes? We're operating under the five minute rule.

Ms. PELOSI. Thank you very much. Thank you, Dr. Klausner.

Mr. PORTER. Mr. Stokes.

CANCER IN MINORITIES

Mr. STOKES. Thank you, Mr. Chairman.

Last year, we discussed the fact that overall African-Americans have the highest death rates from cancer. While much of this reflects a very high rate of cancer among African-Americans males. Can you bring us up to date on specific research and outreach efforts that are underway which are specifically designed to address this very critical national situation?

Dr. KLAUSNER. It is a very critical national situation, and we've done much this year. The most important starting point is to have good information. And tomorrow, we will be releasing what we think is a landmark document which for the first time looks at 12 different ethnic and racial groups, and completely analyzes the incidence and mortality of cancers. There are some very interesting issues here. We need to have this information to guide us about the questions, the research questions we need to ask. This will be released tomorrow. As you know, this is Minority Cancer Awareness Week.

The Office of Cancer Communication has been in collaboration with 166 community organizations around the country in order to provide information specifically aimed at minority and underserved communities to raise awareness about cancer, about what can be done to make sure that cancer is diagnosed early, and especially that cancer, once diagnosed, is followed up.

We have a large number of studies that are going on to deal with the issue of whether these changes in incidence are due to different occupational exposures, different environmental exposures, dietary differences. We are also, for example, supporting on prostate can-

cer, several specific projects asking whether the molecular basis for the progression of prostate cancer in African-American males is different than in Caucasian males.

What is essential if we're going to make progress is to make sure that African-Americans and other minorities participate in research at all levels and are specifically participating in clinical trials. We've just recently finished analyzing that issue for treatment trials in the cancer program, and I'm pleased to tell you that our analysis demonstrates that because of a lot of work done over the last several years, the proportion of minorities that are participating in NCI treatment trials around this country are proportional to the incidence of disease in those populations.

We are not doing well in prevention trials, but we need to now know that, and now we're focusing on what we can do to make sure that minorities and specifically African-Americans participate more fully in prevention trials.

Mr. STOKES. I believe it is important for African-Americans to participate, in particular, in biomedical research and also in the decision making process, especially since, they suffer disproportionately from cancer.

Dr. KLAUSNER. That's right. As I described before you came in, we've set up a whole new series of advisory boards and advisory panels, working groups, review groups, and we are working with the Intercultural Cancer Council, and other groups to make sure that in each of these groups, the interests, the needs and the concerns of the underserved and minorities are represented.

And we have done that. We have made sure that the institution is available to work with the community to hear those concerns. We will soon be setting up a new office in the Office of the Director to deal with special populations.

Right now, the Associate Director for Planning, Dr. Ed Sondik, is finishing a report to me about what the needs are for the institution to make sure that there is greater participation and, more importantly, that we are addressing all of the research issues.

Mr. STOKES. Dr. Klausner, the five year cancer survival rate for the general population is 56 percent. And, that for African-Americans falls significantly below this. Last year, the Institute indicated that for African-American females it was 46.9 percent, and 37.9 percent for African-American males. How are you utilizing this information to help chart the direction of the Institute's research, research training and its outreach initiative?

Dr. KLAUSNER. Again, the critical thing is, we know those numbers. We need to know them well. We need to know how they distribute through the population in order to be able to formulate the questions as to why. Let me give you an example.

It turns out there's an increase, a particular increased incidence of prostate cancer in African-American men in the southeast. It turns out 40 percent of that increase perhaps can be explained by farming, individuals engaged in farming. And that's led us to look specifically at the question of pesticides and insecticides, herbicides, as potentially causative in this increased incidence.

And that's the type of thing we have to do. We now know those numbers, those differences are unacceptable. We have to know

them well, we have to know how they distribute, so that we can design research projects to answer why.

PROSTATE CANCER IN MINORITIES

Mr. STOKES. I have time for one or two more questions, then I have to leave. Let me ask you this quickly. You've mentioned prostate cancer, as you may know this is an area that we've had conversation about in previous years. Considering the fact that African-American males have the highest prostate cancer rate in the world, are we making any progress at all in terms of trying to ascertain the reasons for it, and are we making any progress in how to treat it and so forth?

Dr. KLAUSNER. We've made very little progress in treatment of advanced prostate cancer. The key right now is to make sure that prostate cancer is diagnosed early and then to find out whether our interventions, be they radiation or surgery, are in fact effective at reducing mortality.

We have a variety of large scale studies looking at that, and we have several studies aimed specifically at looking at prostate cancer in terms of its development, in terms of risk factors, in terms of whether PSA can be used identically or not in the African-American population as in the Caucasian population. These are being done through a variety of cancer center mechanisms, as well as a special cooperative group study, looking at the characteristics of prostate cancer and its response to therapy, particularly radiation therapy, in a particular cooperative group that we have.

Mr. STOKES. Thank you, Dr. Klausner.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

CANCER RESEARCH AT FCRDC

Dr. Klausner, one of the unique features of your Institute is the fact that a significant share of your intramural research program is conducted off campus in Frederick, Maryland, through a contract. How did this contract mechanism develop historically? Why was it thought desirable to hire outside scientists to operate your intramural program?

Dr. KLAUSNER. I'm not sure I can give a great explanation for all the decisions that went before me. But let me tell you how we're thinking about Frederick. Those components of the intramural research activities that are going on at Frederick that are clearly intramural research have now become reincorporated into the intramural divisions. Some are still using contract mechanism funding. We will gradually be looking at that over the next few years.

But the most important thing is that they are now, they have become integrated and subject to the same budgeting and review processes as the rest of the intramural programs. My plan for Frederick is largely to make sure that it becomes a center, service center, to serve the entire Nation. We've moved already to deal with that, to make it a center for complex genetics, a center for informatics. We have a supercomputer there, and we are now developing a plan so that that supercomputer links together the clinical center at the NIH with the intramural program with all cancer centers.

We've proposed that to the cancer center directors. They're very interested. And I think that's what Frederick provides us an opportunity to become, not as a center that simply serves the intramural program, but as a center that serves the entire Nation in developmental therapeutics, in developmental diagnostics, in animal models, in complex genetics and in computing and informatics.

Mr. PORTER. The Bishop Calebresi panel recommended moving a portion of the operations from Frederick back to the NIH campus. Are you doing that also?

Dr. KLAUSNER. Yes, we are. We are doing that, but we're doing that through a process of careful review. We have a new board of scientific counselors, and they will be reviewing every program over the next six to nine months that we would consider moving.

And we really feel that it's important that we carefully review the programs in terms of their resources, in terms of the quality, so that first of all, all the individuals are dealt with fairly, dealt with due process, and that we can best look at all of our needs before we make decisions just simply to move things.

NCI BUDGET ISSUES

Mr. PORTER. The Bishop Calebresi panel made several other recommendations, one to reduce the portion of the NCI budget allocated to intramural research from 25 percent to something more in line with the NIH average of about 11 percent, and another to reduce the size of the intramural AIDS program, transferring those funds to extramural AIDS activities at NCI and other institutes. Do you expect to implement those changes, Dr. Klausner?

Dr. KLAUSNER. We already have. The AIDS, when I started, there was approximately \$32 million in the research project pool. I, as well as everyone else, felt that was too little. Just in the last nine months, we've switched that so that there's now \$93 million in the RPG pool. The intramural budget has gone from approximately \$138 million to \$66 million for AIDS.

[CLERK'S NOTE: Subsequent to the hearing, NCI corrected this figure to \$108 million for the record.]

Dr. KLAUSNER. We have created an AIDS malignancy working group. AIDS malignancy is going to be an important focus of the NCI's approach to cancer. And we've created a variety of new approaches to deal with AIDS malignancy, most of which are extramural.

So in fact, as of today, our distribution of AIDS monies in the intramural program is approximately 50 percent as opposed to more like 15 percent when I started, extramural versus intramural.

For the total intramural program, as a result of our reviewing the whole intramural program, creating new zero based budgeting and cost management principles, the current fiscal year 1996 percent of the total NCI budget that is intramural is 18.8 percent, and it will be 17.4 percent in the fiscal year 1997 budget.

AIDS DRUG DISCOVERY PROGRAM

Mr. PORTER. The report from the Levine Panel evaluating NIH AIDS research recommended a significant decrease in the NCI AIDS drug discovery program, because they felt it duplicated in-

dustry work. Do you plan to reallocate these funds, as the panel recommended, and how much funding is involved?

Dr. KLAUSNER. There's approximately \$15 million to \$20 million involved. And it's integrated into the larger NCI drug discovery program. I am not going to actually make significant movements on that immediately. And the reason is, that we have an eminent external panel that we've put together from industry and academia to review our whole drug discovery program. And I want to wait until the report of that committee before I make decisions about where we should be going and what our relationship to industry should be in terms of drug discovery at the NCI.

MIDDLE EAST CANCER INITIATIVE

Mr. PORTER. One of the very innovative things that you've done is to put together a Middle East cancer initiative, which I think offers great promise in improving the health status of that region, and bringing together opposing forces in a greater common cause that they can all ascribe to. Can you tell us where this initiative stands at the moment, and how you are defining NCI's broader international role?

Dr. KLAUSNER. I think NCI does have an important role in the international effort to eradicate cancer. The Middle East Cancer Consortium was proposed by me as a mechanism of bringing that region together to deal with all aspects of cancer. An agreement has now been reached, has been agreed upon by all of the parties involved, and that's Turkey, Cyprus, Israel, the Palestinian Authority, Jordan and Egypt.

Other entities have expressed a desire to participate, and that's Oman, Tunisia and Qatar. And we are now simply awaiting a date for a signing ceremony. This will in fact be the first ministerial level agreement, multilaterally, in the Middle East. We are now using this model and have been talking with representative countries in Asia to also help them with the development of regional cancer consortiums.

Our role is very much advisory and guidance. And one of the things that we can do is hook other organizations, other countries, into the very extensive NCI education, information and informatics system, which really becomes the backbone for their ability to develop such international collaborations. So we hope to have this signed soon.

Mr. PORTER. Was Greece invited to join the initiative?

Dr. KLAUSNER. Greece was not invited to join the initiative. The initiative was not by invitation, it was set up. The participants were self-chosen. And they very much wanted to feel that it was entities that have not been part of many of the European initiatives in cancer that, for example, Greece has been part of.

Mr. PORTER. If Greece wanted to join, would they be welcome to join?

Dr. KLAUSNER. As far as I was concerned, we'd be delighted.

Mr. PORTER. Thank you, Dr. Klausner.

ASHKENAZI JEWS STUDY

Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman.

Dr. Klausner, yesterday we discussed with Dr. Collins of the National Institutes for Human Genome Research the complicated social, ethical and legal issues posed by the discovery of certain disease genes.

With all the new genetic information available through testing, particularly testing now available for the BRCA1 mutation found in Ashkenazi Jews, I'm very concerned about what the National Cancer Institute is doing to ensure that this information is used properly. In fact, in talking to some of the directors of major hospitals in the New York area, they are not doing this test because of concern that the information is not ready to be released, that there is not adequate counseling available.

My question to you is, what action is being taken? Would you like to see a legislative remedy to early release by any institutions or entities of the tests? Do you think there should be action by the FDA and Dr. Kessler? I know you are, doing a lookback study now with regard to the gene, and that the first sample was very small. So we're concerned about all the implications of this, and I'd be interested in your suggestions.

Dr. KLAUSNER. There's two aspects to these implications. One of the aspects relates to legal and social issues of discrimination, employment discrimination, insurance discrimination, and that will have to be addressed legislatively.

There's another very important issue and that is, is this information good, is it worthwhile, how will it be given to individuals. Will it be done in the context of counseling, and will we be prepared to learn the answers to the questions that we and any individual would want to know as part of their decision whether they should be tested. Because if you can't do anything about it, why should you be tested, other than living with this sword over your head.

That is an area we can act on. What we have done is establish, not only for breast cancer, but for all issues of cancer genetics, a cancer genetics network. The point of this network is to create a disseminated system that will incorporate, again, multiple communities, especially health care providers throughout this country, so that we will take the responsibility to make sure that we provide up to date information and education for a medical community that frankly is not prepared for this new world of genetics.

But we have to work with that. So the point of this network is to create the identification of health care providers that will take the responsibility to help educate about counseling, about protocols, about when to test and when not to test.

And in addition, this network will hopefully provide a completely confidential, completely protected mechanism through which we can identify individuals who want to be identified, so that those individuals can participate in the many clinical studies and clinical trials that we're going to have to do to answer the questions we want, such as, does surveillance work, what type of surveillance, what about prevention, what treatments are best?

This is all new, and we need to now get in front of the curve by creating an infrastructure that deals with all of the issues, including everything from information, education, counseling and learning the answers that are raised by these discoveries.

Mrs. LOWEY. I just want to understand. I believe you said you would take responsibility for disseminating this information and working with this health care network. This is not necessarily inclusive of all health care deliverers.

Dr. KLAUSNER. No.

Mrs. LOWEY. So that in other words, if a health care deliverer chooses to go out on his or her own and provide this service with counseling that may or may not be effective, currently you don't have restrictions, it's all voluntary?

Dr. KLAUSNER. It's all voluntary. And perhaps that's how it should be. And the way we're working is with patient groups, with advocacy groups, with all professional societies that we can, bringing them to the NCI to say, we have to do this together. And it has to include societies such as the AMA; it has to include family practitioners, gynecologists; everyone has to be involved.

And the idea then is that we will have a directory of individuals throughout this country that are members of this network. And we have to do it by advertising, to let everyone in this country know that if you're thinking about information, there's a place to call. It will be a toll free number, and they can find out who in their community or who nearby their community is part of this network. Where we can say, or the NIH can say, these are members of a network that are participating in, providing this information in the context of education, of counseling, and the latest information.

Mr. PORTER. Thank you, Mrs. Lowey. We're going to have a third round, it will be a three minute round. But we'll do that.

PROSTATE CANCER

Mr. Stokes.

Mr. STOKES. Thank you very much, Mr. Chairman.

Dr. Klausner, let's go back to your earlier comments relative to the prostate cancer. Let's take a look at the general population this time. I've seen a number of documentaries, news shows, and so forth on cancer, and it appears that there is still a great deal of indecision with reference to treating prostate cancer.

For instance, I've seen programs where they now say that in terms of surgery, doctors are backing away from recommending surgery for prostate cancer. They are saying that even if you have surgery, you're going to have a recurrence in five years. In other cases, they recommend that if you're 70 years of age or older, you ought not to have surgery, you ought to consider hormonal treatment, or in some cases, do nothing. Then, you hear about the freezing treatment, radiation treatment and other modalities.

Tell us, what is the situation? What do we know about prostate cancer?

Dr. KLAUSNER. Well, you've hit the nail right on the head. We don't know the answer to those questions. It seems like we should. Prostate cancer is a very complicated disease, some of which spreads and grows and some of it just sits there. We know that many individuals with prostate cancer probably do not have to be treated.

How are we going to get the answers to those questions? We are doing several large scale studies. One of the most important, I think, is the study done in collaboration with the VA that is asking

the question: "what is the difference in outcome once prostate cancer's been diagnosed of treating it versus simply watching and waiting", and carefully monitoring the patient to see if there's any evidence of the cancer spreading; in this case, generally by following the PSA.

We feel like we should know the answer to that, but we don't. We actually do not know yet which individuals should be treated and how. And so what we're left with is the need to do this research, which we're doing, and the need to make sure that physicians and individuals receive the best information where they can make decisions together about the pros and cons for them of surgery versus waiting versus radiation, versus other therapies.

MRI'S FOR DETECTING BREAST CANCER

Mr. STOKES. While I wasn't here this morning when you made your presentation, I was just looking at the charts dealing with the imaging technologies which you used during your presentation. It appears to be a vast difference between mammography and the magnetic resonance imaging. Is magnetic resonance imaging much better than mammography? Are we moving towards trying, then, to have greater utilization of that technology?

Dr. KLAUSNER. This is more of anecdotal example, it's a proof that it can be possible. But only now are we beginning to set up the clinical trials to find out in how many women this works. Now, this is a younger woman, and what you can notice is, the breast is very dense. And our suspicion is, this technology is going to be particularly helpful in women in whom mammography is particularly difficult, and that's generally younger women, because of breast density.

And so we will be doing those studies to learn how effective MRI is versus how effective standard mammography is versus how effective digital mammography is, and in which populations of women.

Mr. STOKES. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

PRIVATE GIFTS AND GRANT FUNDING

We will now have a three minute round. And let me begin with a question. Last year, much attention was given to the \$100 million gift to the University of Utah for cancer research by John Huntsman. A gift that size raises the question as to whether NCI adjusts its research portfolio priorities to account for substantial non-Governmental support in certain research areas.

Do you plan to decrease your investment in the research areas designated by the Huntsman gift, or reduce NCI funding of researchers at Utah, since they are receiving a large infusion of private funds?

Dr. KLAUSNER. No, we don't. Probably half of that money will be spent on a building. But basically, we will continue to fund what we feel is important and high quality through our standard peer review. We applaud the Huntsman family and any others that are willing to contribute to discoveries in medicine and cancer.

It is clear that we cannot, with our resources, fund all of the excellent ideas in all excellent areas. And in fact, cancer research, as

with all research, is a partnership between many, many participants, many components. And they in fact do not compete with each other, but rather, they work very well to complement and enhance each other.

CHAMPUS SUPPORT OF CLINICAL TRIALS

Mr. PORTER. As Dr. Varmus mentioned in his testimony last week, the Defense Department health insurance program, CHAMPUS, will now reimburse NCI for its patients participating in clinical trials. What significance does this have, both in terms of financial benefits to the Institute, and the precedent it may set for other insurers?

Dr. KLAUSNER. It's not that they're reimbursing NCI. What they do is that they agree to pay the clinical costs associated with being evaluated for and participating in any NCI-sponsored clinical trial, treatment trial in cancer phases two or three.

Now, these are—and in fact, it specifically excludes the trials going on at the clinical center. In this, the patients will be seen at institutions throughout the country using the disseminated NCI clinical trial system, which involves something like over 2,000 hospitals and over 6,000 physicians. There are something like 400 different protocols.

These patients will be identified and the beauty of it is that this is a completely disseminated network, and they can identify where the closest institution is for the study that they're going to participate in. The NCI does not get any of this money. It is to the institutions that are seeing the patients in the clinical trials.

GRANT APPLICATION STIMULI

Mr. PORTER. Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman.

Dr. Klausner, in your experience, do the number of research applications increase when NCI is able to fund a higher percentage of grants which have passed the peer review process? In other words, if you're able to fund a greater percentage of grants in prostate cancer or breast cancer, will that mean that you're going to get a greater number of grants in that particular area?

Dr. KLAUSNER. I don't know the exact numbers, but my feeling is that the most dramatic stimulus to investigator-initiated grants in any particular area turns out to be the perception in the community of the scientific opportunities. We can make adjustments here and there, and it often feels like we're making more adjustments than we are.

But I've been in the scientific community, I've spent my life there. It is clear that you respond when you see there's an opportunity for discovery. And in this year, it may be here, and next year it may be there. And that, more than anything else, drives what individuals are truly putting in their grant applications for.

Mrs. LOWEY. I think I've used my three minutes.

Mr. PORTER. I'm sure you haven't.

THE INTERNET AND SCIENTIFIC RESEARCH

Mrs. LOWEY. I really appreciate it. One of the things that's always interested me was the burst of energy and information on the internet. How has that contributed to that process of generating scientific research? I was listening one night to National Public Radio at 1:00 in the morning, and the inventor of the World Wide Web was saying that people are just leapfrogging ahead in research and sharing information on the internet. So I just wonder about that. How does that affect scientific possibilities?

Dr. KLAUSNER. I think it's dramatically affecting it in all sorts of ways. It's changing how we communicate, it changes how quickly we can communicate. It changes the fact that now communication is really two way rather than just reading something and then stopping. We're all in this rapidly changing world. And frankly, while being part of it, I think we can only imagine the ways in which the internet is going to change things.

But there is no question that our ability to finally deal with informatics, that not only allows things to happen quicker and better and cheaper, but even creates possibilities that weren't created before, is entirely new, with the Web and the Internet. That's an entirely different, it's a quantum leap in our ability to exchange information. And we're using it extensively.

And the wonderful thing about it is that it's a very cottage industry phenomenon. People set up Web sites for breast cancer mutations. A new one just went up this week. And it is profoundly enhancing communication, which is very much at the core of our success in research.

Mrs. LOWEY. Well, I just want to assure you in conclusion that, again, I think I said this earlier, if it were up to our Chairman and myself, and I know I would speak for Mr. Stokes, as well we would greatly increase the resources of NIH so we could greatly increase the research applications and perhaps end the scourge of breast cancer, prostate cancer and all these diseases that plague our society.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mrs. Lowey.

Mr. Stokes.

GENE THERAPY RESEARCH

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Klausner, how critical is gene therapy research to furthering advances in areas of research which are under the purview of your Institute?

Dr. KLAUSNER. Gene therapy research is connected to the most fundamental research in understanding how the cell works. We have, as Dr. Varmus' committee pointed out this year, we have a long way to go before the promises of gene therapy are going to be fulfilled in terms of affecting patients with particular diseases. But it is clear to all of us that at some point, we don't know when, we are going to get there.

And so gene therapy research is important to do now. But what's important to do is to do the step by step foundational research so that we learn about how to manipulate genes, how we might de-

liver genes, how we might control that delivery, so that in the future, we actually can think about using gene therapy. So I think it's going to be very important, but there's a long way to go.

Mr. STOKES. Can you tell us what diseases and disorders would benefit from enhanced research?

Dr. KLAUSNER. Well, I think it's conceivable that most diseases can benefit and for cancer, there's a variety of different approaches to gene therapy. One is to replace a gene that's defective. And that, while we might know the genes, we don't yet know how to deliver them.

Another major area of research that relates to gene therapy in cancer actually relates to immunotherapy, and trying to find ways, through genetic manipulation of cancers or of immune cells, to enhance the probability and the effectiveness of the immune system in rejecting and attacking cancer. That's a very different type of gene therapy, and perhaps may be the more proximate gene therapy that we'll see tested for cancer.

CANCER DETECTION

Mr. STOKES. I understand that cancer cells can be anywhere in the body, and may never accumulate in sufficient numbers to threaten the health of the individual, and may be undetectable with current technology. Is that correct?

Dr. KLAUSNER. That's correct.

Mr. STOKES. What progress are we making with respect to being able to improve this type of detection and diagnosis?

Dr. KLAUSNER. That's a very interesting area. And we think that what we're referring to as the post-genome world is going to provide us some very exciting possibilities there. We know, because the genes that are expressed in cancer cells are different than their normal counterparts, that there ought to be gene products that will allow us the possibility of creating a new type of detection technology.

I have an advisory group specifically, that's the advisory group chaired by Dr. Arnie Levine, that is going to help the NCI work on how we're going to use what we know from the genome to move into this post-genome world to try to identify those molecular markers that will allow us to know when these hidden cancer cells are in the body.

Mr. STOKES. Thank you very much, Dr. Klausner.

Mr. PORTER. Dr. Klausner, as I said earlier, we very much appreciate the tremendous enthusiasm and the innovation and creativity you bring to the directorship of NCI. And we think your testimony today was excellent and we appreciate your coming before the committee to enlighten us.

Dr. KLAUSNER. Thank you very much.

Mr. PORTER. Thank you so much.

[The following questions were submitted to be answered for the record:]

COORDINATION OF CANCER RESEARCH

Mr. Porter: Last year the Subcommittee expressed concern about lack of coordination of cancer research activities across all sectors, public and private. What steps have you taken to re-establish coordination of cancer research activities?

Dr. Klausner: We believe that coordination across all sectors is vital to the success of the National Cancer Program. In working with the President's Cancer Panel, we have developed a plan to create a National Cancer Council, a group that will represent a full range of public and private sectors including research, the voluntary organizations, the pharmaceutical industry, insurance and health care providers, professional organizations, and the public. It will bring together all constituents with interest in the outcome of a national cancer effort, as well as other sectors with an interest in the health and welfare of the nation. We have formulated a mission charge to the council and identified a key aspect of the council's operation, namely, that it must operate in a way that it is as free of institutional biases as possible. We believe that an appropriate venue for the council is the National Academy of Sciences and are now working with the Academy leadership to develop a plan to implement the Council as an academy round table. We believe that this mechanism will catalyze and enable communication between the sectors, and be the ideal setting for discussion of such critical issues as cancer screening, pain management, information dissemination, and achieving state-of-the-art detection and treatment.

NCI FUNDING POLICIES

Mr. Porter: Dr. Klausner, the controversy last year associated with your funding of the tobacco company campaign contributions grant did, among other things, raise the question of what NCI's mission should be in its funding of cancer prevention research. Do you and your Advisory Council intend to review the definition of NCI's mission to provide clear standards on what biomedical and behavioral research NCI will use its scarce resources to support?

Dr. Klausner: It is clear that with finite resources we cannot support all aspects of cancer research. To identify those aspects that are the most critical, we have set in motion five comprehensive reviews of critical areas of cancer. These include cancer centers, clinical trials, prevention, developmental therapeutics and cancer control. Each of these groups has been charged to outline the areas it considers the most critical to make progress against cancer. Another committee, under the auspices of the National Cancer Advisory Board, is reviewing behavioral research and its relation to cancer and is well aware of my concerns and your concerns on the limits of cancer research. The results of the behavioral science review will be forwarded to the cancer control review and to the cancer prevention review and their results, in turn, to the scientific advisory boards and the NCI Executive Committee. I am confident that our emphasis on the importance of fundamental research coupled with these reviews will provide the guidelines and recommendations for funding future research that will provide the greatest

contributions to knowledge, knowledge that is critical to fighting cancer.

NCI's RELATIONSHIP TO OTHER AGENCIES

Mr. Porter: Is it an appropriate standard to say that NCI should focus its efforts on research that other agencies do not have the expertise to support?

Dr. Klausner: NCI's mission is clear: To focus its resources on biomedical and behavioral research that is fundamental to understanding cancer and to developing ways of preventing, detecting, and treating this constellation of diseases. Our standard must be to support research that scientists, through peer review, feel is most critical to the effort. If an aspect of important biomedical research can be supported under the mandate of another agency, we will endorse their effort. However, we must not diffuse our resources by funding activities that more appropriately fall within the mission of other agencies of lower priority research. It would be preferable for such agencies to acquire the requisite expertise in-house to support research within their mandates.

PREVENTION AND CONTROL SET-ASIDE

Mr. Porter: Would you recommend to our authorizing committees at they amend or repeal the current statutory set-aside to spend 10% of NCI funding on cancer prevention and control?

Dr. Klausner: Cancer Control efforts are directed primarily on research on the behavioral, psychosocial, health services, communication and cancer surveillance aspects of translating proven technologies and testing methodologies into routine practice in the community. This would include a focus on population groups who bear excessive risks for cancer or who lack access to state-of-the-art cancer services. The efforts supported through the NCI's Cancer Control program are very important to the entire National Cancer Program. The NCI is committed to further developing our efforts in this arena and I do not feel that maintaining a portion of the NCI budget as a percentage set-aside to be used exclusively on Cancer Control is necessary. The preference is to provide the Director with resource flexibility to allocate funds among all NCI programs based on scientific merit and need.

SEATTLE FIELD STATION

Mr. Porter: You have funded a research project in Seattle that has received press attention because of its unconventional structure as an intramural grant operated by extramural researchers. Why didn't you support this project as a regular extramural research grant?

Dr. Klausner: The NCI conducts a worldwide search for chemicals and natural product sources that can be tested in its screening systems for the identification of new drugs active against cancer. Many drug companies and individual investigators submit their products to the screen after signing a legally

binding agreement with NCI that their own intellectual property claims on these products will be honored and protected by the NCI. The project in Seattle involves a quite novel approach for identifying new drugs that may be active against human cancer. It utilizes yeast, a common organism whose genes and biochemical pathways have been very well characterized by scientists over the past few years. Despite obvious differences between yeast cells and animal cells, it turns out that yeast strains with mutations in certain pathways bear significant similarities to cancer cells. It may be possible, therefore, to use these similarities to identify active anticancer drugs, and NCI wanted to add this capability as quickly as possible to our standard screens. We decided to create an intramural "field station" in Seattle for two principal reasons. First, if the Seattle project were conducted as an intramural effort, rather than under grant support, there would be no intellectual property barriers to transferring any chemical submitted to the NCI screen to Seattle for testing there. The data from the Seattle tests are then transferred back to Bethesda for analysis and for integration with the data generated by the other parts of the drug screen. Secondly, we anticipated that, once the screening methods in yeast had been fully developed by this group (2-3 years), the technology would then be transferred to Bethesda or Frederick for on-line use in the intramural drug-discovery program. In order to ensure that the Seattle project was rigorously reviewed prior to allocation of funds, the proposal was sent to three outside reviewers who are internationally known authorities in the subject area. Their critiques of the project were evaluated by the NCI Executive Committee and, on the basis of these critiques, the proposal was further strengthened.

NCI BYPASS REINVENTION

Mr. Porter: Dr. Klausner, another area where you are reinventing is the NCI Bypass Budget. The current version seems to be a fraction of the size of its predecessors. What are your objectives in the presentation of the Bypass Budget with this new format?

Dr. Klausner: This Bypass Budget is different in several respects from prior NCI submissions. We have developed this document to be easier to understand and to highlight the major opportunities available today for cancer research. It is responsive to the desires of the cancer research community for a more user-friendly document that clearly portrays the opportunities and needs of the cancer program. It provides a clear description, for multiple audiences, of not only the requirements of a maintenance level request, but the clear articulation of five high-priority program areas for an increased investment opportunity. The resource level proposed, while still substantial, is not as large an increase as may have been presented in previous years.

The first level or maintenance level is essential to assure stability, continuity, and progress in NCI's existing research program in laboratory, clinical, and population studies aimed at the prevention, detection, diagnosis and treatment of cancer and the rehabilitation of cancer patients.

The second level, or Investment Opportunities, permits expansion into crucial new areas of research. The proposed additional investment will augment the core research program across the spectrum of cancer biology, cancer risk, cancer intervention and cancer control. We have identified five areas of research opportunity which will greatly increase our capacity to reduce suffering due to cancer. The five program areas that deserve immediate investment are: Cancer Genetics, Preclinical Models of Cancer, Detection Technologies, Developmental Diagnosis, and Investigator-Initiated Research, to support the opportunities for discovery that will be created, in part, by these new initiatives.

NON-PROFIT CANCER FUNDING

Mr. Porter: What is the total funding of cancer research by the various non-profit associations and philanthropies?

Dr. Klausner: While the Cancer Institute does not have direct access to funding information for the various non-profit associations and philanthropies, we are aware that the American Cancer Society (ACS) funded research totaling more than \$94 million in 1995. Other funding of which we have knowledge includes \$1.4 million per year for research training funded by the American Society of Clinical Oncology (ASCO). Other organizations funding cancer research may include, but are not limited to, the American Association for Cancer Research (AACR), the Leukemia Society of America, the American Society of Hematology (ASH), the American Institute for Cancer Research, the Cancer Research Institute, the Damon Runyon-Walter Winchell Cancer Research Fund, the Jane Coffin Childs Fund for Medical Research, and the UICC - International Union Against Cancer. In addition, many private hospitals, including St. Jude's in Tennessee, are heavily involved with cancer research efforts.

NIH DIRECTOR'S RESERVE PLANS

Mr. Porter: Explain how you plan to spend the funds reallocated to NCI in the Director's one percent transfer proposal.

Dr. Klausner: Under the NIH Director's one percent transfer proposal, the NCI budget was reduced by \$3.0 million as its contribution to the establishment of the NIH Director's 1% transfer fund. NCI was then allocated \$10 million from the NIH for a net increase of \$7.0 million. Most of this support will be utilized through the Clinical Cooperative Group program and the Cancer Centers network - for informatics development and genetics research. NCI plans to put in place a national informatics infrastructure for clinical trials. This program will improve quality, reduce paperwork, ease monitoring and link databases for DNA and tissue repositories, correlative markers and epidemiologic studies.

With the impending ability to identify those individuals with a genetically determined predisposition to cancer, NCI is prepared to use funds received to establish a Cancer Genetics Cooperative Group. This will provide individuals

expanded access to genetic testing for cancer within the context of counseling and clinical research. A portion of the funds received will be used to create Technology Development Centers. These Centers will stimulate technology and applications to enable molecular advances to translate to patient care by providing such services as genotyping, mutation analysis, gene expression analysis, functional assays, and whole genome screening for potential tumor biomarkers.

COST OF INTRAMURAL LABS

Mr. Porter: What is the average and range in the cost of NCI intramural labs for FY94 and FY95?

Dr. Klausner: The fair and appropriate allocation of intramural resources, a basic tenant of the Bishop-Calabresi report, was a cornerstone of the new Intramural Organization and Principles (IOP) manual recently developed to establish uniform policies for the scientific management of the Intramural Research Program (IRP). The principles reflected in the IOP were an outcome of a Director's Retreat held in the early stages of NCI's reorganization, which established a firm foundation for scientific review, management and allocation of intramural resources to our labs. One of the specific outcomes of the Intramural Retreat was the establishment of cost principles by which to evaluate resources and to allocate future budgets at the principal investigator level rather than at the lab/branch level. Site review criteria were also developed that incorporate an assessment of resource allocation in relation to scientific accomplishments, again at the PI level. These changes have had a significant impact on the overall resources that were allocated to the Divisions, Lab/Branches as well as the individual Principal Investigators, in fiscal year 1996.

Based upon this new approach, for this year, *principal investigator* budgets range between \$85 thousand and \$1.9 million in the clinical branches, while the basic research PI's range from \$85 thousand to \$1.8 million. These figures include all support for salaries, supplies, services, travel, equipment, research support contracts, and many patient related activities.

REDUCTIONS TO INTRAMURAL LABS

Mr. Porter: Were any reductions made to individual lab budgets as suggested in the Bishop-Calabresi report?

Dr. Klausner: As I indicated in my response regarding the average and range in the cost of intramural labs, the NCI has established important new guidelines to improve resource stewardship as an outcome of the Bishop-Calabresi recommendations. There are new cost principles that impact the allocation of funds, as well as improved fiscal accountability through budgets allocated at the level of each principal investigator (PI) responsible for conducting research in the intramural program. These new costs principals, along with the formal recommendations emanating from the site visit review process, were used by the intramural Division Directors to establish appropriate budgets for intramural labs/branches, at the principal investigator level. The impact of these principles has been a number of reductions to overall Laboratory budgets as well as specific PI budgets. Labs and branches received reductions in their budgets ranging from 1% to 38%. Additionally, one basic research laboratory has been closed as a result of a site visit, and the closure of a clinical research branch has been approved and is underway.

CENTERS PROGRAM BUDGET STRUCTURE

Mr. Porter: What changes are you contemplating in the structure and budget of your cancer centers program?

Dr. Klausner: The cancer centers are, to the consumer and the researcher, one of the most visible and accessible parts of the NCI. To address the issues raised by your question, I have convened a committee of outside experts to review the entire cancer center program. I have asked this committee to review and evaluate the entire centers program and make recommendations on how this program might be strengthened and adapted to current needs. This review is coming at a crucial time for the centers; along with academic health centers generally, the NCI-supported cancer centers are facing unprecedented challenges to their mission because of major changes in patterns of reimbursement for clinical care. In particular, we have asked this advisory group to address how the NCI can help assure centers maximal flexibility in the use of NCI support for their research infrastructure, while at the same time ensuring that the process of peer review can be conducted in an orderly, non-arbitrary fashion. We expect that the committee will make its report to the NCI by the fall of 1996. This report will then be discussed by the NCI's major advisory boards - the Board of Scientific Advisors and the National Cancer Advisory Board - and by the leadership of the institute. Institution of changes in the program will follow.

H. PYLORI

Mr. Porter: In 1994, an NIH consensus development conference endorsed the findings that *H. pylori* is strongly associated with peptic ulcers. Was your Institute involved in the research that led to this finding?

Dr. Klausner: The bacterium *Helicobacter pylori* infects the gastric mucosa of humans and is present in a large proportion of the world's population. Chronic infection with *H. pylori* can lead to gastric and duodenal ulcer disease, chronic gastritis, and possibly gastric cancer. Eradication of the organism has been shown to induce long-term remission of peptic ulcer disease, but the pathogenesis of the organism in other gastric conditions and its etiological relationship to malignancy has not been clearly determined.

As early as 1983, in Shandong Province, a rural area of northeast China, where the stomach cancer rates are among the highest in the world, the National Cancer Institute has been collaborating with the Beijing Institute for Cancer Research to assess the risk factors associated with this disease and to test means for its prevention. Initial findings showed increased risks associated with consumption of salt and a fermented local food (i.e., sour pancakes), while reduced risks were related to intake of allium vegetables (e.g., scallions and garlic) and beta-carotene and vitamin C-containing fresh fruits and vegetables. In a gastroscopic screening program, chronic atrophic gastritis, an early precancerous lesion, was found in almost the entire adult population. This screening program also found *H. pylori* infection linked to early stages of chronic atrophic gastritis and to its progression to more advanced disease.

On October 16, 1993, the NCI sponsored a workshop entitled "Helicobacter and Cancer." The purpose of the workshop was to assess the then current state of knowledge on the role of *H. pylori* in gastric cancer in humans. Participants were asked to determine whether there were basic science laboratory-based research areas that needed stimulation in the form of grants or contracts. The consensus view that resulted from the workshop was that while *H. pylori* appeared to have a role in some malignancies, additional studies of this organism and related bacterial species were necessary to clearly define their relationship to human gastric and other cancers.

On the basis of these recommendations, the NCI issued a Request for Application (RFA) for \$1.5 million/year for four years. A sister institute, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), expressed a strong interest in the initiative and offered to provide \$500,000 toward the project and cosponsor the RFA. The joint RFA was issued on May 20, 1994. Twenty-seven applications were received with proposals ranging from basic molecular studies to animal models of human disease. In 1995 NCI funded eight meritorious applications at a first year level of \$1.59 million.

Among the funded extramural grants is a natural history study in an Indian and Hispanic population in the Yucatan region of Mexico that has an extremely high rate of preneoplastic gastric lesions and stomach cancer. Another project studies the biology of gastric lymphomas. Other projects are using animal models to study chemical carcinogens in *Helicobacter*-associated malignancies. Additional investigations will determine whether *H. pylori* strains obtained from gastric cancer patients are distinct from those obtained from patients with nonmalignant gastroduodenal disease such as gastritis and peptic ulcer disease. These research efforts will expand our knowledge of the role of *Helicobacter* in the etiology of peptic ulcers and human cancer.

EDUCATION EFFORTS - H. PYLORI

Mr. Porter: Are you involved in any public education efforts in this regard?

Dr. Klausner: Efforts are continuing to educate scientists, medical practitioners, patients, and the general public about *H. pylori* and its relationship to human disease. As a result of the NCI workshop entitled "Helicobacter and Cancer", a meeting report was published in the Journal of the National Cancer Institute in October, 1994. Additionally, an NCI Cancer Information Service booklet dealing with risk factors for stomach cancer describes *H. pylori* and is made available to patients, the general public, and appropriate medical groups. Also, the NCI, through its 1-800-4-CANCER telephone activity, makes available to the public the most recent information on risk factors for gastric cancer, including information relating to *H. pylori*. Furthermore, the NCI physicians data query system (PDQ) also cites this bacterium as a risk factor for stomach cancer, and that information is publicly available through the Internet.

PROSTATE CANCER INITIATIVES

Mr. Porter: Prostate cancer is now the most commonly diagnosed cancer in America according to the American Cancer Society. Have you planned new initiatives to address the problem of prostate cancer?

Dr. Klausner: The Cancer Institute recognizes the magnitude of the problems faced with prostate cancer. It affects nearly 245,000 men each year. In addition to the basic research that has applicability to prostate cancer as funded by investigator initiated grants, the Institute has identified special initiatives in this area as well. Successful treatment of prostate cancer requires the ability to distinguish indolent prostate cancers better left untreated from aggressive disease requiring treatment. Both types are common. Successful treatment of advanced disease requires new approaches.

The Institute began planning the Prostate, Lung, Colon and Ovarian Cancer Screening Trial in 1988. This trial, which was implemented in 1993, is designed to answer the question, "Does prostate cancer screening with serum prostate specific

antigen, or PSA, save lives?" In 1993 the NCI launched the Prostate Cancer Prevention Trial to determine if the drug finasteride will decrease prostate cancer risk. Both these trials will also contribute to our abilities to understand the disease at a genetic level. The Prostate Intervention Versus Observation Trial, or PIVOT, began in 1995. It assesses the efficacy of radical prostatectomy, the most common treatment for localized prostate cancer.

The Specialized Programs of Research Excellence, or SPORes, integrate clinical trials and laboratory research. Three universities have SPORes grants devoted to prostate cancer research. A number of smaller NCI sponsored clinical trials and basic laboratory efforts are ongoing.

The Intramural program of the NCI is expanding its search for the molecular genetic events with the development of prostate cancer. In a collaborative effort among scientists in the NCI's Surgery Branch and Laboratory of Pathology, as well as scientists from the National Center for Human Genome Research, new molecular techniques are being applied to the study of the genetic events associated with initiation as well as progression of human prostate cancer. This multidisciplinary approach is employing newly developed, sophisticated technology in this research.

A new unit, Developmental Molecular Diagnostics, has been created within the Laboratory of Pathology in the Division of Clinical Sciences to translate this new genetic information into better methods for staging and early diagnosis of prostate cancer. This collaborative group has identified a new area on chromosome 8 which is considered fundamental to the development of the earliest forms of prostate cancer.

PROSTATE CANCER FUNDING

Mr. Porter: Do you expect to allocate additional resources to the problem in 1997?

Dr. Klausner: Yes, the NCI expects to allocate additional resources to the problem of prostate cancer in 1997. The NCI estimate for prostate cancer research in 1997 is \$72.2 million. This is an increase of 2% over the current 1996 estimate and a 10% increase over what was spent in 1995.

NEUROFIBROMATOSIS RESEARCH

Mr. Porter: We understand that the neurofibromatosis (NF) research field has produced some important discoveries in the past several years and is poised to make advances in treatment. What level of support do you plan to commit to NF research in 1997, including any joint efforts with other Institutes?

Dr. Klausner: In FY 1997, NCI estimates that it will devote \$5.9 million to neurofibromatosis research. NCI's multi-disciplinary collaborations throughout the NIH and the extramural NF research community are included within this figure.

NEUROFIBROMATOSIS RFA

Mr. Porter: Last year's House report suggested that you consider issuing an RFA for NF research. Do you think this is a good idea?

Dr. Klausner: I recently received a copy of a letter sent to the NIH Director regarding neurofibromatosis research. The letter, from Dr. Bruce Stillman of Cold Spring Harbor Laboratory, presents the results of a conference held last Fall on "Neurofibromatosis: How to Develop Therapies." Dr. Stillman is also a member of the newly established NCI Board of Scientific Counselors. As a result of this conference, the NF community of basic scientists, clinicians, and representatives of large pharmaceutical firms has decided to establish small working groups whose charge is to solicit consensus opinion on research needs in NF, particularly in translational and clinical research, and develop recommendations for the NIH. The issuing of an RFA is a possible outcome. It is anticipated that the Institutes would work individually, or together, as appropriate, to develop the most effective approach for addressing these identified research needs, using input from the working groups. This approach has some very exciting possibilities since it originates with the involved research community. The NCI experience has found investigator-initiated research to be a most productive avenue of discovery. Thus, we have not ruled out the use of an RFA or an additional program announcement to further exploit research opportunities in this field, but we do not consider it necessary at this time in view of the ongoing, NCI-funded investigator-initiated efforts.

COORDINATION OF PREVENTION AND CONTROL

Mr. Bonilla: Dr. Klausner, last year the Committee expressed its support for the National Cancer Advisory Board's 1994 report entitled "Cancer at the Crossroads" which concluded that the national cancer program suffered from a lack of coordination of cancer fighting efforts in the public, private and voluntary sectors. As a result the Committee recommended that NCI take the lead in coordinating the nations cancer prevention and control programs with CDC and other Federal agencies to reestablish coordination of the national cancer program. Could you outline for us your efforts over the past year to accomplish this recommendation?

Dr. Klausner: We believe that coordination across all sectors is vital to the success of the National Cancer Program. Working with the President's Cancer Panel, we have developed a plan to create a National Cancer Council, a group that will represent a full range of the public and private sectors including research, voluntary organizations, the pharmaceutical industry, insurance and health care providers, professional organizations, and the public. It will bring together all constituents with an interest in the outcome of a national cancer effort, as well as other sectors with an interest in the health and welfare of the nation. We have formulated a mission charge to the council and identified a key aspect of the council's operation, namely, that it must operate in a way that it is as free of institutional biases as possible. We believe that an appropriate venue for the council is the National Academy of Sciences and are now working with the Academy leadership to develop a plan to implement the Council as an academy round table. We believe that this mechanism will catalyze and enable communication between the sectors, and be the ideal setting for discussion of such critical issues as cancer screening, pain management, information dissemination, and achieving state-of-the-art detection and treatment.

CANCER RESEARCH RELATING TO SEXUAL ORIENTATION

Mr. Dickey: National Cancer Institute scientist Dean Hamer has conducted two studies in an attempt to find evidence for a "gay gene." It is my understanding that he is now under investigation for fraud in the first of the two studies. Another Hamer team member, Angela Pattatuci, is conducting a search for a "lesbian gene." Is NIH diverting taxpayer money from cancer research toward the quest for "gay genes"?

Dr. Klausner: Thank you for the opportunity to clarify this matter. Dr. Dean Hamer is Chief of the Section on Gene Structure and Regulation, Laboratory of Biochemistry, Division of Basic Sciences, National Cancer Institute. Dr. Hamer's research on sexual orientation was conducted as part of NIH Clinical Protocol #92-C-0078: "Genetic Factors and Interrelationships for Sexual Orientation, HIV Susceptibility and Kaposi's Sarcoma, Alcoholism and Related Psychopathology, and Histocompatibility Antigens."

The primary purpose of this research was to better understand and treat cancer. The focus was Kaposi's sarcoma, a malignancy that occurs in HIV-positive homosexual men but not in seropositive parenteral drug users, hemophiliacs or women, nor generally in members of the general population. There was evidence to suggest that susceptibility to Kaposi's sarcoma might be genetically influenced and Dr. Hamer's group studied families in which two or more homosexual brothers were at risk for Kaposi's sarcoma. It was during the course of this study that a statistically significant linkage between sexual orientation and DNA markers on the X chromosome was discovered. Dr. Hamer published these findings as well as those found in a second study, with data from new subjects, that substantiated his original publication.

This study was completed in 1994 and no further funds were used in studies that are classified as "sexual orientation" studies since that time. The DNA samples collected for that project have been used to look for potential genetic risk factors for disease (HIV/AIDS) progression.

Dr. Hamer's research has also included a study of genetic factors and potential relationships between female sexual orientation and breast cancer. A published study suggested that lesbians may have an elevated risk of contracting breast cancer. Dr. Angela Pattatucci, a postdoctoral scientist in Dr. Hamer's laboratory, studied this problem in 1994 but this study required resources that were not available to the Laboratory, and the project was terminated in 1995 and Dr. Pattatucci left the NCI.

Dr. Hamer is a brilliant scientist who has made many important contributions. He is searching for genes that predispose to cancer such as attempting to discover why only 20% of heavy smokers develop lung cancer. He has recently discovered a genetic locus that is associated with a personality trait that is correlated with cigarette smoking and other addictive behaviors (Benjamin *et al.*,

Nature Genetics 12, 81-84, 1996). A similar finding has been reported independently by another group. This may lead to improved strategies for intervention in patients at risk for developing cancer.

Dr. Hamer is one of a handful of scientists attempting to find links between behavior and cancer risk until now only referred to anecdotally. From the onset, NCI realized that this research would attract attention, but the protocol used in his studies was thoroughly reviewed. There was and has been no attempt to conceal the nature of the research nor to "divert" funds. It is the aim of the NCI and of all the NIH Institutes to provide the best possible health research for all Americans.

P-20 PLANNING GRANTS

Mr. Dickey: It is my understanding that the "P-20" planning grants are 3 year grants which were designed to encourage some cancer research programs to eventually move up to "P-30s" which are "NCI designated Cancer Centers." Is this correct?

Dr. Klausner: You are correct. The purpose of the P20 planning grant is to help institutions develop the capability to become NCI-designated Cancer Centers by competing successfully in our peer review process for a Cancer Center Support Grant (P30).

P-20 PROGRESS

Mr. Dickey: How many P-20s have improved status from P-20 to P-30 in the past 3 years?

Dr. Klausner: At this time, approximately half of the P-20 grantees have applied for Cancer Center Support Grants and some of these are in the process of reapplying. The NCI poses no restrictions on how often an institution can apply for a P-30. No grantees have improved status from P-20 to P-30 at this point in time.

P-20 EXTENSIONS

Mr. Dickey: Do you ever extend P-20s to allow them to apply more than once to become a P-30?

Dr. Klausner: Many of the active P20 planning grants have been extended for an additional year, often with funds, either because the planning and development process required more time than originally predicted or in order to provide an institution another opportunity to apply for a P30.

IMPROVEMENTS IN BREAST CANCER TREATMENT

Mr. Dickey: I read in a Washington Post article dated March 27, 1996, that researchers are discovering that milk duct breast tumors may not always require

mastectomies, rather, lumpectomies are often effective. This seems to be a tremendous breakthrough. What is NCI's position and its role in researching the treatment of milk duct tumors?

Dr. Klausner: Cancer of the milk ducts of the breast is the most common type of breast cancer. For invasive cancers of this variety, randomized studies supported by NCI and others have shown that lumpectomy and breast irradiation yields equivalent survival results to mastectomy. The Washington Post article referred to an article in the Journal of the American Medical Association that appeared the same day. The article reported a study that addressed the incidence of non-invasive breast cancer of the milk ducts. It showed a significant decline in the number of mastectomies being done for this condition in 1992 when compared to figures from 1983. This trend would appear to be continuing today and it is true that far fewer women are undergoing mastectomy. The NCI continues to support additional research in this area designed to answer whether there is a need for breast irradiation in women with this disease or is lumpectomy alone sufficient.

AFFIRMATIVE ACTION

Mr. Stokes: What progress has the institute made with respect to the recruitment and involvement of African American, hispanic and other disadvantaged populations in biomedical research, and the NCI's planning and decision making?

Dr. Klausner: The Institute has been very active over the past year in developing an affirmative action plan, called the "Work Force Equity and Diversity Action Plan," or "WEDA Plan," that encompasses diversity goals for all disadvantaged populations. This plan was carefully crafted through the involvement of multiple working groups, made up of a representative group of NCI staff. Workgroup membership was culturally diverse and included representatives from all grade bands and job series. These groups used historical data relating to hiring, selection, and retention as well as U.S. national and regional census data to develop recommendations for affirmative action goals in all job series across the NCI, including scientific positions. The WEDA Plan outlines specific employment goals for under represented targeted groups for both scientific and administrative positions within the Institute and places the responsibility for reaching those goals on individual managers, supervisors, and selection officials. The plan was developed with significant emphasis on streamlining targeted recruitment efforts, and placing the primary responsibility for achieving and maintaining a diverse work force on those who have the hiring authority, that is, selecting officials and line managers.

These goals are now being used to develop appropriate recruitment, career development and training programs at the NCI. The plan will be monitored and evaluated in a number of ways, including tracking numbers and sources of applicants from targeted groups, numbers hired, promoted, and trained, and comparing that to the number of opportunities. Recruitment strategies will also be evaluated, including the success of specific recruitment activities developed as a result of the WEDA Plan, on-site visits, the standing NCI recruitment registers, and targeted mailings. The affirmative action plan is effective through September 30, 1996 at which time an evaluation will be made regarding NCI's efforts in achieving these goals.

During the past year the NCI has also been very active in establishing groups to represent all employees in policy and program development. The NCI has developed an Intramural Advisory Board--IAB--and an Extramural Advisory Board--EAB--to provide advice to the Director on ways to sustain and create an effective research infrastructure. The NCI is looking at ways of changing and improving the role of the Equal Employment Opportunity Advisory Group in NCI operations and facilitating its interaction with other advisory groups such as the IAB and EAB. The NCI Director has met with these groups to hear their concerns and to encourage their active role in helping to identify the concerns of employees as well as to develop recommendations the Institute can use in improving EEO and Human Resource activities.

In addition, the NCI established a Special Actions Committee to examine how the Institute should address the concerns of special populations. Such populations are defined as populations which have a disparity in either cancer incidence, treatment, or mortality from the general population. The Committee has also been concerned with the training of minorities both into the general field of medical oncology as well as cancer research. The results of the Committee's deliberations over the past five months will shortly be presented to the NCI Executive Committee for consideration and implementation. We anticipate that as a result of the recommendations expected, that the NCI will establish a senior level office to facilitate and coordinate the Institute's various efforts aimed at encouraging more minority physicians and Ph.D. candidates to pursue careers in biomedical research.

ENVIRONMENTAL CAUSES OF CANCER

Mr. Stokes: What percentage of cancers are attributed to environmental causes?

Dr. Klausner: It has been estimated that perhaps 75-80% of all cancer is influenced by environmental factors including lifestyle exposures such as tobacco and diet. This estimate is derived from the international variation in cancer incidence and mortality, along with pronounced shifts in cancer risk among population groups migrating from low-risk to high-risk countries.

NCI COLLABORATIONS WITH NIEHS

Mr. Stokes: For the record, provide a detailed description of the collaborative activities which are underway between NCI and the NIEHS?

Dr. Klausner: Within the intramural research program, NCI and NIEHS are collaborating in the Agricultural Health Study, which is a prospective cohort investigation involving 75,000 farmers, their spouses, and commercial pesticide applicators in Iowa and North Carolina. The project provides the opportunity to evaluate occurrence of cancer and other diseases in relation to various agricultural exposures, including pesticides, engine exhausts, fuels and oils, and dusts. NCI is taking the lead on studies of cancer, while NIEHS is focusing on non-malignant outcomes. Enrollment of the cohort will be completed by the end of the calendar year, and plans for the second five years of follow-up are being developed.

In another intramural effort, NCI and NIEHS are collaborating on a biomarker project to investigate genetic susceptibility and mechanisms of action of environmental carcinogens. Components of this project include genetic polymorphisms and DNA adduct formation and bladder cancer risk among persons exposed to benzidine; hematotoxicity and genetic polymorphisms among individuals exposed to benzene; and mutagenicity, urinary metabolites, and genetic polymorphisms related to heterocyclic aromatic amine exposure.

Extramurally, collaborative activities between NCI and NIEHS support research in advancing methodological applications in molecular and environmental epidemiology. Areas of interest include the development of biomarkers for etiologic research of prostate cancer and geographic information systems for assessing association of environmental factors and breast cancer risk. The mechanisms of collaboration involve the development of Requests for Applications (RFAs) and Program Announcements (PAs), and co-funding of grants. Specific areas of collaborative cooperation include the following:

RFA CA/ES-92-23 issued July 31, 1992; Funded 1993-1996 "Biotechnology Transfer to Epidemiologic Studies in Cancer"; 4 R01 grants funded by NCI; 4 R01 grants funded by NIEHS. Joint meeting of investigators in September 1994 and planned for in 1996. Objective: validation and application of biological markers in etiologic cancer research

RFA CA/ES-93-024 issued March 19, 1993; Funded 1993-1997 "Environmental Factors and Breast Cancer in High-Risk Areas"; 6 U01 projects co-funded by NCI and NIEHS. Joint meetings of investigators October 1993, May 1995, planned in July 1996. Objective: response to Congressional mandate regarding high breast cancer incidence and mortality rates in the Northeast and Mid-Atlantic regions of the United States

RFA CA/DK/ES-94-028 issued August 5, 1994 by NCI, NIDDK, and NIEHS "Molecular Epidemiology of Prostate Carcinogenesis"; 4 R01 grants co-funded by NCI and NIEHS, 1995-1999. Objective: development of biochemical and molecular markers for identifying and assessing risk factors for prostate cancer

PA-95-032 issued February 10, 1995 by NCI and NIEHS "Geographic Information Systems in Environmental Health Sciences". Applications due February 1, June 1, October 1 of each fiscal year. Objective: response to Congressional mandate (Public Law 103-43) to investigate role of environmental factors and high breast cancer mortality rate in Long Island, New York

PA-95-084 issued August 18, 1995 by NCI, NIDDK, and NIEHS "Molecular Epidemiology of Prostate Carcinogenesis". Applications due February 1, June 1, October 1 of each fiscal year. Objective: to continue solicitation of grant applications proposing development and utilization of biomarkers in prostate cancer research

PA-96-008 issued December 1, 1995 by NCI and NIEHS "Epidemiology of Lung Cancer: Interdisciplinary Studies". Applications due February 1, June 1, October 1 of each fiscal year. Objective: to better understand etiology of adenocarcinoma and small cell carcinoma of the lung

P01 ES/CA06409; co-funded by NIEHS and NCI 1992-1996 "Molecular and Genetic Analysis of Lung Cancer"; Harvard University. Objective: program project elucidating possible susceptibility risk factors of lung cancer by use of

molecular markers

U01 CA/ES66572; co-funded by NCI and NIEHS 1995-1999 "Breast Cancer and the Environment on Long Island"; Columbia University. Objective: population-based case-control study, a core component of the Congressionally mandated Long Island Breast Cancer Study Project (LIBCSP), evaluating environmental factors and breast cancer risk in Long Island, NY

"Registry of Tumors in Lower Animals". This contract is a unique information resource on neoplasms in lower animals. It maintains an aggregate of expertise in the taxonomy and anatomy of lower animals unavailable elsewhere. It facilitates the study of neoplasms and related disorders in lower animals by serving as a centralized repository of pathologic materials, a diagnostic center, and an information resource.

In addition to the above intramural and extramural research projects, NCI and NIEHS participate jointly in the following activities:

NCI Chemical Selection Planning Group--CSPG: This group guides program staff in reviewing, selecting and prioritizing chemicals for evaluation by the Chemical Selection Working Group prior to nominating them to the National Toxicology Program for carcinogenicity testing; in providing chemical production, use and exposure information to the International Agency for Research on Cancer and in maintaining the Chemical Carcinogenesis Research Information System.

NCI Chemical Selection Working Group--CSWG: This group evaluates, selects and prioritizes candidate chemicals for nomination for carcinogenicity testing by the National Toxicology Program.

National Toxicology Program--NTP--Interagency Committee for Chemical Evaluation and Coordination: This committee evaluates and selects chemicals nominated by Federal and state agencies, trade and labor unions, scientific research organizations, and private citizens for testing by NTP; evaluates the NTP chemical selection process, as appropriate.

NTP Executive Committee: This committee provides primary program oversight to the NTP (represents the NCI Director).

NTP Working Group for the Biennial Report on Carcinogens: This expert interagency NTP committee evaluates lists of candidate chemicals for inclusion in the DHHS Biennial Report of Carcinogens.

Interagency Coordinating Committee on the Validation of Alternative Methods--ICCVAM: This expert interagency NTP committee develops recommendations relating to the validation and acceptance of new and revised testing methods that would reduce the utilization of test animals and be useful to Federal agencies--Congressional mandate.

National Toxicology Program Annual Plan: Members of the NCI staff write responses and testing summaries for Part 2 of the NTP Annual Plan, *Review of Current DHHS, DOE, and EPA Research Related to Toxicology*. The Chemical and Physical Carcinogenesis Branch is coordinator of the NCI report for FY96.

EPA TSCA Interagency Testing Committee: This committee makes recommendations to the Administrator, EPA, regarding chemical substances and mixtures to which the Administrator should give priority consideration for the promulgation of a rule for testing under Section 4 of the Toxic Substances Control Act--TSCA.

MINORITY OUTREACH ACTIVITIES

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your institute?

Dr. Klausner: The NCI established a Special Actions Committee to examine how the Institute should address the concerns of special populations. Special populations are those which have a disparity in either cancer incidence, treatment, or mortality from the general population. The Committee has also focused on training opportunities for minorities in both general medical oncology and cancer research. The results of the Committee's deliberations over the past five months will be presented shortly to the NCI Executive Committee for consideration and implementation. We anticipate that as a result of the recommendations, the NCI will establish a senior level office to facilitate and coordinate the Institute's various efforts aimed at encouraging more minority physicians and Ph.D. candidates to pursue careers in biomedical research.

This year, NCI published several Request for Applications--RFAs--to promote minority participation in cancer research. The first is the "Minority Enhancement Award," which invites research grant applications from interested investigators with access to large or predominantly minority populations to promote minority group participation in cancer research, with a special focus on cancer control research. General research objectives within the scope of this initiative include, but are not limited to, studies of smoking behavior in minority youth; studies of communication strategies for presenting information to minorities about cancer and its prevention; investigations of patient perspectives of cancer risks; the design and evaluation of interventions to minimize and control distress of minority patients with cancer; the development of pilot studies for minority clinical prevention trials; and psychosocial studies and perception of cancer risk in minorities.

Another RFA, "Minorities in Medical Oncology," is intended to encourage recently trained under represented minority clinicians to acquire clinical training and research in clinical oncology and to increase representation of minorities in clinical oncology. This award is designed to provide an intensive, supervised clinical and

research experience for under represented minority physicians. Specifically, these awards will provide the opportunity for recent, clinically trained under represented minority physicians and Doctors of Osteopathy--D.O.s--to gain sufficient research and clinical experience to become practicing clinical oncologists with experience in biomedical research.

Two other new grant programs, while not designed specifically to fund minority physicians, will fund physicians caring for large numbers of minority patients. Since many minority patients seek care from minority physicians, announcements for request for applications--RFAs--have been targeted to minority physicians and institutions, with assistance in publicizing the RFAs coming from the Intercultural Cancer Council. NCI has advertised these *Women and Minority Recruitment* programs for the purpose of developing strategies to improve enrollment of women and minorities in cancer prevention and screening clinical trials. The first RFA under this program, the Small Grant Program, has invited applications to perform pilot studies, test new ideas, or gather information that will lead to the development of effective models and strategies to improve the participation of women and minority groups as subjects in cancer prevention and screening Phase III research. The second RFA under the Women and Minority Recruitment program, Intervention Testing, invites investigator-initiated grant applications--R01s--for research to develop, implement, and test well-defined, hypothesis-based interventions to improve the participation of women and minority groups as subjects in cancer prevention and screening clinical trials. The proposed research will build on current knowledge and research findings concerning clinical trial participation and patient recruitment, compliance, retention, and physician referral factors, and will focus on Phase III research.

In addition to these new initiatives, the NCI has a number of ongoing programs aimed at increasing the number of minority cancer researchers. Under the Research Supplements for Under represented Minorities Program, NCI-funded Principal Investigators are invited to apply for supplements to their existing grants for the support and recruitment of under represented minority investigators and students. The aim of these supplements is to attract and encourage minority individuals to enter and pursue biomedical and behavioral research careers in areas within the mission of the National Cancer Institute. Another ongoing program is designed to encourage undergraduate and graduate students to pursue training related to cancer research. The NCI Comprehensive Minority Biomedical Program--CMBP--co-funds, with the Minority Access to Research Career--MARC--Program of the NIGMS, pre-doctoral fellowships to minority students and honors undergraduates training grants to minority institutions. This arrangement has facilitated the establishment of invaluable liaisons with the minority academic community and enabled NIH as a whole to support a major source of trained or trainable minority scientific personnel. Similarly, through another co-funding agreement with NIGMS's Minority Biomedical Research Support--MBRS--program, NCI provides support for specific cancer-related projects at participating minority institutions for the purpose of assisting faculty and students to develop biomedical research capabilities.

Other ongoing programs include the NCI/MARC Summer Research Training Program, through which the NCI supports conferences and research training for minority individuals and institutions to further enhance the mission of the National Cancer Institute. This program is designed to increase research training opportunities for under represented minority scholars through the influence of short-term laboratory training. Another program provides travel fellowships for minority pre- and post- doctoral students to attend annual meetings of the American Association for Cancer Research--AACR. The AACR Minority Scholar Travel Awards are intended to increase the attendance of minority scientists at the national meeting and to stimulate the participation of pre- and postdoctoral minority students in cancer research. Students participate by giving scientific presentations, poster sessions, and other activities.

Other NCI minority-targeted programs, while not designed specifically to fund minority physicians or researchers, include the Minority-Based Community Clinical Oncology Program--CCOP--which provides funding to institutions and consortiums where more than 50 percent of the new cancer patients are from minority populations. This year, 10 Minority-Based CCOPs are funded to accrue participants to cancer treatment, prevention and control trials. They are located in nine states and Puerto Rico. The program now involves more than 40 hospitals and 350 physicians, including African-American and Hispanic investigators. In addition, the Eastern Cooperative Oncology Group, from its Minority-Based CCOP cooperative agreement, has hosted meetings with National Medical Association--NMA--chapters in a number of cities including Oakland, Cleveland, Indianapolis, and Philadelphia. The purpose of the meetings is to make these physicians aware of opportunities to participate in NCI-sponsored cooperative group clinical trials. NCI staff continue to meet with NMA members at their national meetings to foster collaborations and to encourage participation in research.

The Institute has been very active over the past year in developing an affirmative action plan, called the "Work Force Equity and Diversity Action Plan," or "WEDA Plan," that encompasses diversity goals for all disadvantaged populations. This plan was carefully crafted through the involvement of multiple working groups, made up of a representative group of NCI staff. Workgroup membership was culturally diverse and included representatives from all grade bands and job series. These groups used historical data relating to hiring, selection, and retention as well as U.S. national and regional census data to develop recommendations for affirmative action goals in all job series across the NCI, including scientific positions. The WEDA Plan outlines specific employment goals for under represented targeted groups for both scientific and administrative positions within the Institute. These goals are now being used to develop appropriate recruitment, career development and training programs at the NCI. The affirmative action plan is effective through September 30, 1996 at which time an evaluation will be made regarding NCI's efforts in achieving these goals.

During the past year the NCI has also been very active in establishing groups to represent all employees in policy and program development. The NCI has developed an Intramural Advisory Board--IAB--and an Extramural Advisory Board--EAB--to provide advice me on ways to sustain and create an effective research infrastructure. The NCI is looking at ways of changing and improving the role of the Equal Employment Opportunity Advisory Group in NCI operations and facilitating its interaction with other advisory groups such as the IAB and EAB. I have met with these groups to hear their concerns and to encourage their active role in helping to identify the concerns of employees as well as to develop recommendations the Institute can use in improving EEO and Human Resource activities.

MORTALITY RATES: LUNG VS. COLORECTAL CANCER

Mr. Stokes: According to your opening statement, deaths from colorectal cancer have dropped due to better therapies, while deaths from lung cancer are rising among women. How many Americans die from lung cancer, as opposed to the number who die from colorectal cancer?

Dr. Klausner: Approximately 145,000 people, both men and women, die each year of lung cancer while 60,000 people die from colorectal cancer each year.

FUNDING: LUNG VS. COLORECTAL CANCER

Mr. Stokes: How much is included in the FY 1997 budget request for each of these cancers, and how does it compare with the funding level for FY 1996 and FY 1995?

Dr. Klausner: The FY97 budget request includes \$120 million for lung cancer research. This is an increase of 3% over the FY96 estimate and an increase of 5% over the \$114 million spent in FY95.

NCI estimates spending \$102 million for research on colorectal cancer in FY97. This represents an increase of 3% over the 1996 estimate and 5% over FY95 spending.

DIETARY GUIDELINES FOR AFRICAN AMERICANS

Mr. Stokes: What progress do you have to report regarding the "culturally sensitive intervention strategies for implementation of the NCI dietary guidelines among African Americans?"

Dr. Klausner: We have launched a new initiative that encourages investigator-initiated grant applications for studies to develop and evaluate the effectiveness of culturally sensitive intervention strategies to assist African Americans in adopting eating patterns consistent with the NCI Dietary Guidelines.

Specifically, the research focuses on four areas: (1) identification of barriers and motivators of dietary change among African Americans; (2) development of culturally sensitive intervention strategies to increase knowledge and promote attitude and dietary behavior change among African Americans; (3) evaluation of the effectiveness of culturally sensitive intervention strategies in achieving and maintaining eating habits consistent with the dietary guidelines; and (4) evaluation of the impact of dietary changes on biochemical and anthropometric parameters. To date, a total of 13 applications have been received and reviewed for scientific merit through the NIH peer-review process. It is expected that three applications will be awarded in the spring of 1996.

OUTREACH AND PUBLIC EDUCATION ACTIVITIES

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at your institute?

Dr. Klausner: The NCI developed the Cancer Information Service (CIS) infrastructure 20 years ago to bring new science and important NCI messages directly to the public. As a program of the NCI, the Cancer Information Service has ready access to cutting-edge research. The CIS takes complex cancer research and treatment information and translates it in a way that is accurate, unbiased, understandable, and meaningful for all audiences served. For example, the public has a direct link to the science through CIS information and referrals to both prevention and treatment clinical trials.

Through the Cancer Information Service, a network of 19 regional offices serving the 50 United States and Puerto Rico, the public can seek out the latest cancer information, in English or Spanish, by calling 1-800-4-CANCER. CIS developed an outreach program to bring information to under served and minority communities through partnerships with community groups who have access to these special populations. The regional structure enables the CIS outreach program to bring NCI messages into communities across the country in a way that no national-level campaign could.

Major educational initiatives developed by NCI and distributed through the CIS and other partners include:

BREAST AND CERVICAL CANCER EDUCATION PROGRAM

The Institute continues its mammography education activities with the development, promotion and dissemination of audience specific materials. The materials support many nationwide education activities carried out by the CIS outreach coordinators and federal, state and local agencies, local community groups, service organizations, churches, and local health facilities. Specifically, NCI is developing resources for community-based organizations to assist them in planning their breast cancer and mammography education and outreach programs. To support

the breast cancer program, NCI also conducts media activities, including provision of resources and media support for National Minority Cancer Awareness Week (NMCAW) and National Breast Cancer Awareness Month (NBCAM)

NCI produces cervical cancer education resources such as the 9-minute video entitled, "Taking Control of Your Health: The Pap Test and Cervical Cancer." It is the first culturally-appropriate, inter-tribal videotape on cervical cancer, which is more prevalent in American Indian women. In clear, simple language, it offers an overview of the disease, an explanation of the Pap test, recommendations for screening, and possible ways to prevent the disease. It is for women of all ages, from sexually active teens to post-menopausal women. The film was introduced at a national meeting of Native American women, and is being distributed with its original musical score and support materials through Native American intermediaries. NCI continues distribution of several basic print brochures on cervical cancer for special audiences, including low-literacy African-American, and Hispanic women.

PROSTATE CANCER EDUCATION PROGRAM

To respond to the needs of the community, NCI has developed several fact sheets on prostate cancer. In addition, NCI gathered information on men's attitudes, concerns, understanding and behavior regarding prostate cancer in preparation for a new brochure, which is under development.

NUTRITION PROGRAM

The Institute's program on nutrition offers information on the relationship between diet and cancer and offers dietary steps for lowering the risk of cancer. The 5 A Day for Better Health effort remains the cornerstone of the program.

Scientific evidence indicates that people who eat larger amounts of fruits and vegetables have a lower risk of cancer. The 5 A Day for Better Health program, a partnership with the Produce for Better Health Foundation, is a national consumer education program to encourage Americans to eat 5 or more daily servings of fruits and vegetables.

NCI continues to promote the Institute's dietary guidelines and nutrition messages by distributing education materials to intermediaries and the public. NCI distributes several nutrition education materials designed for the general public, African Americans, and Hispanics. In addition, NCI has developed a series of nutrition education materials for low-literacy segments of specific ethnic populations. These populations include American Indians, Alaskan Natives, Hawaiian Natives, Chinese, Filipinos, Vietnamese, Hispanic, African-Americans, and whites. These materials are now in design prior to publication.

SMOKING PROGRAM

NCI continues its tobacco education efforts, emphasizing communications support for the Institute's American Stop Smoking Intervention Study (ASSIST) program. Other initiatives included DCPC's smokeless tobacco campaigns with Major League Baseball and Little League Baseball.

The National Cancer Institute believes that a significant fraction of cancer mortality can be eliminated with aggressive application of existing knowledge. The NCI's Leadership Initiatives on Cancer are clearly a response to research findings that strongly show that many cancers are the result of lifestyle, attitude, and behavior. Achievement of these goals depends primarily on the Initiatives' ability to involve community leaders in cancer prevention and control issues; build lasting community cancer prevention and control coalitions; and, transfer cancer research findings to community settings.

The National Black Leadership Initiative on Cancer (NBLIC) has been working since the late 1980s to promote cancer control and prevention in Black communities. The program has developed strong networking relationships with national, state, local, grassroots, and special interest organizations across the United States. A major focus for NBLIC is the establishment of community-based cancer prevention and control coalitions. One area of emphasis includes the objectives of the DHHS Healthy People 2000 initiative, which gives priority to reduction of cigarette smoking; increasing breast cancer screening; reducing fat intake; and developing and implementing a national process to identify gaps in disease prevention and health promotion data on Black Americans.

The Minority Health Professions Foundation is the current grantee for the NBLIC Project. The national program consists of multiple components: 1) coalition building through identification and recruitment of new organizations and new local leaders; 2) strengthening the capacity of existing coalitions through leadership training, small grant opportunities, dissemination of project findings and centralized database management; 3) promotion of the long term sustainability of coalitions through regional training, formalization of coalition structure and identification of long term funding prospects; 4) changing knowledge levels, attitudes and behaviors with regard to cancer through the standardization of health education content; and 5) monitoring the effectiveness and impact of the project throughout all phases through comprehensive process and outcome evaluation using qualitative and quantitative measures.

The National Hispanic Leadership Initiative on Cancer (NHLIC) is a major outreach program that extends across the nation. The NHLIC engages a team of high-caliber researchers committed to deliver the most efficient and appropriate cancer intervention research and outreach programs to Mexican Americans, Cuban Americans, Puerto Ricans, and Central and South Americans. It also strives to achieve and surpass the Healthy People 2000 cancer objectives for Hispanic

Americans. As a result of a 1989 RFA, two five-year cooperative agreements (U01s) were awarded: one to the University of Texas Health Science Center in San Antonio, Texas, project known as *En Acción*, and the other to the National Coalition of Hispanic Health and Human Services Organizations, known as COSSMHO, in Washington, D.C. The *En Acción* project is analyzing the post-intervention survey data to gauge the effectiveness of their community-based outreach intervention strategies on improved knowledge, attitudes & behavior regarding cancer screening & care, as well as build coalitions for dissemination, institutionalization and policy advocacy. There will be a symposium in August 1996 at the University of Texas, San Antonio, to highlight the community based infrastructure of the *En Acción* model, its products, preliminary findings, partnerships and institutionalization.

The Appalachia Leadership Initiative on Cancer (ALIC) is designed to facilitate the development of a strong cancer control network in Appalachia. Because the incidence and mortality rates for some cancers are disproportionately high among Appalachians, NCI created ALIC as one of its community outreach initiatives. Pennsylvania State University, West Virginia University, University of Kentucky, and North Carolina State University, working cooperatively with other regional, state, and local agencies, are partners in this effort. The ALIC mission is to enhance the capacity of rural Appalachian communities to implement and maintain local cancer control programs. These grassroots efforts help residents to become more aware of when and where to seek early detection for cancer, how to proceed when cancer is diagnosed, how to navigate through an increasingly complex and technical health care system, and where to turn for community resources and support for survivors.

The ALIC coalitions draw on the combined resources and support of other NCI programs, including the Cancer Information Service (CIS), the National Black Leadership Initiative on Cancer, the National Hispanic Leadership Initiative on Cancer, the 5-A-Day for Better Health Program, the American Stop Smoking Intervention Study (ASSIST), and national organizations such as the Cooperative Extension System, the American Cancer Society (ACS), and the Centers for Disease Control and Prevention Breast and Cervical Cancer Early Detection Program. The major emphasis is on community-based cancer control activities.

OUTREACH AND EDUCATION FUNDING LEVEL

Mr. Stokes: How much is included in the FY97 budget for the institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Klausner: The National Cancer Institute supports a diverse range of information dissemination programs for many audiences. The dissemination of information regarding all aspects of cancer investigation and care is a crucial priority to NCI. The Institute's obligation is not merely to generate knowledge and publish

it in journals, but also to make sure that the latest information regarding prevention, diagnosis and treatment is being communicated to the public. For that reason, our FY97 proposed funding level is \$185.5 million which is 4 percent higher than the FY96 funding level of \$178.3 million. In FY 1995, the funding level was \$176.5 million. FY97 reflects an increase of 5 percent over FY95 and an increase of over 14 percent from FY94's level of \$162.4 million.

OUTREACH AND EDUCATION FUNDING MECHANISM

Mr. Stokes: In most of the institutes, these programs are funded in research management and support account, is this the case in your institute?

Dr. Klausner: Historically, the NCI funded significant outreach efforts through multiple budget mechanisms, including R&D Contracts, Research Management & Support (RMS) and the Cancer Prevention & Control budget. For example, the 19 regional contracts that comprise the NCI's Cancer Information Service (1-800-4-CANCER) were supported from the contract line. However, the Federal staff overseeing this venture were supported from RMS. Also funded from the RMS budget is the International Cancer Information Center, an organization unique to NCI. This unit developed, and now supports, our on-line PDQ information service on cancer. The Office of Cancer Communications, similar to information offices housed within our sister institutes, is budgeted also from the RMS line. Their efforts include responding to public inquiries, developing programs with the media et al to provide the latest results of our research to the public, significant printing of publications for the general public as well as other community outreach and public education activities. As you are aware, other outreach initiatives such as the National Black Leadership Initiative on Cancer and the Appalachian and Hispanic initiatives were developed and funded through our Cancer Control program. So, while many of our outreach efforts are funded through RMS, it is not the only mechanism. With the recent reorganization of the NCI, we have consolidated most of our information and outreach activities within Cancer Control. This will provide an improved administrative focus and it is an appropriate, I believe, to fund these outreach activities through this vehicle.

OUTREACH AND EDUCATION STATUS

Mr. Stokes: If so, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Klausner: Yes, we have been able to maintain our highest priority areas. The NCI holds the dissemination of research findings to be of high merit and, even though the reductions directed in the RMS budget required difficult choices, we maintained these efforts. However, we continue to take a critical look at all activities to ensure we are operating them as efficiently as possible.

NEEDY OUTREACH AREAS

Mr. Stokes: In which outreach areas are you hurting the most?

Dr. Klausner: I don't believe that NCI is hurting in any specific area. What we need to continue to do is to identify gap areas and develop programs and initiatives to meet the defined need. We will need research into those areas to determine the most plausible approach.

COLLABORATION WITH THE OFFICE OF RESEARCH
ON MINORITY HEALTH

Mr. Stokes: What collaborative efforts are underway between your institute and the Office of Research on Minority Health?

Dr. Klausner: NCI and the Office of Research on Minority Health--ORMH--continue to collaborate on numerous projects. Ongoing efforts last year totaled \$3.9 million.

It has been the practice of ORMH to solicit specific ideas, some of which are independently funded by that office, and some of which are cosponsored. ORMH is often limited to soliciting requests and then dispensing funds one year at a time which leads to awards that are made late in the fiscal year, and limits the suitability of collaboration to short term projects.

Fiscal year 1996 proposed projects have been submitted to ORMH by NCI and are currently being considered. Projects funded in FY95 include:

Minority Adolescent HIV Research Project	\$2,938,483
5th Biennial Symposium on Minorities, the Medically Underserved and Cancer	45,848
U.S./Mexico Border Conference on Women's Health	10,000
Native American Cancer Conference III	50,000
Supplement to Pediatric Oncology Group for recruiting minority patients	228,025
Supplement to grants in Comprehensive minority Biomedical Program (includes students in high school, undergraduate, graduate, and postdoc programs)	439,000
NCI/Howard University collaboration on new chemotherapy agents against metastatic prostate cancer	200,000

OFFICE OF RESEARCH ON MINORITY HEALTH FUNDING

Mr. Stokes: Are there specific projects in your institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Klausner: No NCI projects were funded entirely by ORMH.

PROJECTS CO-FUNDED BY ORMH

Mr. Stokes: Are there specific projects that are co-funded by the institute and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the institute and the office.

Dr. Klausner: NCI has submitted a list of proposed FY96 projects to ORMH which are currently being considered for funding. The projects proposed are:

Adolescent HIV Research Program

Collaborative Clinical/Pharmacologic Research Study of New Chemotherapy Agents Against Metastatic Prostate Cancer

Mentoring & Grants Writing Workshops

Universal Cancer Screening to Improve Clinical Trials Access

Enrollment of Minorities in NCI Clinical Trials

Direct Evaluation of Role of Fatty Acids in Explaining the Differences in Prostate Cancer Risk Between Blacks and Whites

Prostate Cancer Prevention Trial

Loss of heterozygosity on chromosome 8p12-21 in prostate cancer for African-American men versus Caucasian men

Overcoming Impediments to Participation of Minorities and Special Populations in Clinical Trials

Funding dates and amounts for projects supported by ORMH will be determined later in FY96.

GENETIC PREDISPOSITION AND CANCER

Mr. Stokes: What is the association between genetic predisposition and the diseases and disorder under the purview of your institute?

Dr. Klausner: The relationship between genetic predisposition and the many diseases that are called cancer is quite complex. There are two broad classes of genetic susceptibility that are important in cancer causation. The first is single gene traits, where an alteration in a single gene may increase the risk of a specific cancer. Examples of these are retinoblastoma, a rare childhood tumor, and some fraction of breast, ovarian, colorectal, and other cancers. A different type of genetic susceptibility is a change in genes that code for proteins that chemically alter potentially toxic exposures, such as cigarette smoke. Changes in these genes may not be critical in cancer risk unless the person is also exposed to a specific agent. For example, if a person has a change in a gene that is important in detoxifying a cancer-causing chemical but is never exposed to that agent, the change would not alter the individual's risk of cancer. Conversely, if the person worked in an environment where exposure to the chemical occurred, he or she might be more susceptible to developing a cancer.

Genes that are more directly related to cancer, the single gene type, are more easily identified in large families where multiple people have developed the same type of cancer. Examples are the genes for retinoblastoma, Wilm's tumor, breast cancer, colon cancer, and melanoma. The other type of cancer susceptibility gene is most easily identified in studies of large populations, where good exposure and other possible risk information can be obtained. The evaluation of both predisposing gene types is extremely important to understand why specific individuals develop cancer, and how the malignancy develops. When particularly high risk groups are identified, screening and interventions may reduce morbidity and mortality associated with the cancers.

GENE REPOSITORY

Mr. Stokes: What can you tell us about the status of the gene repository as it relates to these diseases?

Dr. Klausner: The identification of genes that are involved in the development of cancer is currently one of the most active areas of research. New genes are rapidly being identified, some of which could be important to our understanding of the causes of cancer. Many of these genes have been found in high-risk families that are predisposed to certain types of cancers. Other cancer susceptibility genes confer a much lower risk, and require large population-based studies to evaluate their untoward effects. Biological materials collected from high-

risk families and participants in larger population-based studies are maintained for research purposes in repositories, which are operated under strict security and confidentiality guidelines.

NCI is currently supporting a major effort aimed at the establishment of a series of multi-center initiatives, the Cooperative Family Registries for Cancer Studies (CFRCS). The Cooperative Family Registry for Breast Cancer Study was funded in FY95, and is now operational. The funding of a Cooperative Family Registry for Colorectal Cancer Studies is planned for FY96. Additional cancer-specific registries are planned for FY97/98. These registries will develop population-based collections of biological specimens and correlated clinical and epidemiologic data on families and individuals from different geographic areas at high and intermediate risk for developing various types of cancer.

GENE REPOSITORY AND MINORITIES

Mr. Stokes: What is the status of the gene repository as it relates to African Americans, and other minorities?

Dr. Klausner: Research on the identification of cancer susceptibility genes is being done in African-Americans, as well as in other racial groups. The identification of specific genetic alterations in a particular racial or ethnic groups may enhance screening opportunities, resulting in measures to prevent or control a cancer outcome. Currently, NCI is working with the National Center for Health Statistics and the Centers for Disease Control and Prevention to evaluate the ability to determine the prevalence of genetic changes in several thousand blood samples collected from the National Health and Nutrition Examination Survey III. Biological samples with genetic material are about one-third African-American, one-third Hispanic, and one-third white. These samples will be invaluable in assessing the frequency of genetic changes that predispose to cancer within each of these groups.

In the Cooperative Family Registries for Cancer Studies, particular emphasis is being placed on enrollment of African-Americans and other minority group members. In addition, the NCI is supporting a pilot study for the collection and storage of biological specimens from African-American families at high risk for breast cancer.

PROSTATE CANCER PROGRESS

Mr. Stokes: I understand that the 1987 Consensus Development Conference on the "Management of Clinically Localized Prostate Cancer" helped the institute to identify "Areas of Research Need" with respect to prostate cancer. It has been nearly a decade since that conference, what progress have we made in prostate cancer since that time?

Dr. Klausner: Twelve clinical and two basic research directions were enumerated in the report of the Conference. A few of these have clearly been rendered less compelling by subsequent developments, particularly accumulated experience with utilizing prostate-specific antigen--PSA--as part of disease evaluation and staging; however, others remain cogent issues. Some of the identified directions can be discussed together because they are naturally linked.

The first three areas of identified needs in Clinical Research concerned improvements in prostate cancer classification, cytologic and pathologic grading, staging, and diagnostic imaging. Since the 1987 conference, sensitive prostate-specific antigen (PSA) assays and sophisticated transrectal ultrasound (TRUS) equipment, and TRUS-guided needle biopsies, have become nearly universally available in the U.S. These have greatly expanded the capacity of community facilities to identify prostate cancer. This, in addition to greatly enhanced public recognition of the disease, has led to a markedly increased frequency of the diagnosis, and increased familiarity of community pathologists with the Gleason pathologic grading system, which is now quite widely utilized. In 1992, the American Joint Committee on Cancer and the International Union Against Cancer adopted a revised staging system, which is clinically useful and more precisely stratifies newly diagnosed patients. Meanwhile, however, another consequence of wide application of PSA screening and TRUS has been a downward stage shift. The majority of cases are now diagnosed with clinically localized disease, often of small volume, and fall into categories of disease with generally favorable natural histories. This has by no means diminished the challenge or importance of identifying higher and lower risk cohorts among such patients, however, without which we cannot minimize therapeutic interventions for those patients with biologically unaggressive, potentially clinically silent, cancers. To this end, a number of retrospective analyses have been performed on a large series of patients seen in major Cancer Centers and NCI Cooperative Groups, and various algorithms developed for combined clinical/biochemical/pathological staging. These are currently being tested and validated in large Cooperative Group trials.

Another clinical research direction noted in the report was the need to assess the availability and quality of surgical treatment. We can report that the rate of surgical treatment has skyrocketed--5.75-fold increase since 1984--as more urologists have had training and experience with retropubic and/or perineal prostatectomy, and with techniques for nerve-sparing. Although this suggests that availability is now quite good, no firm conclusions can be drawn as yet about quality or about the optimal rate of surgical management or patient selection. The Agency for Health

Care Policy and Research--AHCPR--has sponsored research into treatment outcomes in prostate cancer therapy, and one major finding is that there is substantial variation in rates and selection criteria from one part of the country to another, without a definite clinical or scientific basis. There is also a higher than anticipated rate of prostatectomy in patients aged 75 years and older, in whom the complication rate is higher and likelihood of benefit less. These data, as well as U.S and European reviews that identify rough comparability for more conservative approaches, have stimulated major educational programs and provide further impetus to studies designed to attempt to identify which prognostic factors can predict for the need for surgical prostatectomy.

The conference report further identified the need for uniform data reporting to allow meaningful comparisons of treatment by different disciplines. This goal is, if anything, more elusive now than in 1987 because it is now clear than uniform reporting cannot overcome the problem of selection bias inherent in the elective treatment decisions of both patients and clinicians. For example, a structured review of the relevant literature appears to demonstrate that 10-year prostate cancer-specific survival rates were best in surgical series (93%), worst in radiation series (about 75%), and intermediate with no initial treatment at all, other than for symptoms (about 85%). Since it is highly unlikely that radiation would actually worsen disease-specific survival, the most likely interpretation is that selection factors affect choice of therapy. In this case, it is probable that otherwise very healthy and younger patients are offered surgery, patients with generally less advanced cancers are selected for watchful waiting, and patients with bulky or symptomatic cancers in neither of the other categories tend to be managed with radiation. Thus, direct comparative trials will be necessary to resolve the issues. These are difficult studies to do because they are not attractive to patients, but attempts are under way.

Another research need identified was for the identification of low- and high-risk prognostic variables. Clinical and radiographic parameters, Gleason grading, various manipulations of PSA data, morphometric variables, labeling indices, angiogenic indices, molecular phenotypes, cytogenetic changes, and other variables have been formulated into several different algorithms that are being tested and validated in larger series to determine whether they can prognosticate and direct therapy better than simpler staging systems.

The conference report also addressed the need for assessment of the clinical significance of positive post-radiation biopsies and how these may be reduced. It is now recognized that the rate of such positive biopsies is very high following conventional external beam radiation, and that the rate of detectable or rising serum PSA is also very high. In large series, however, some of these patients remain free of clinical cancer recurrence for many years without further treatment. Presently, however, many of these patients receive additional hormonal treatment--often without a biopsy--because of understandable concern as PSA slowly rises. Attempts

to address this whole issue include ongoing randomized trials of hormonal treatment along with external radiation, and attempts to safely augment the radiation dose by using sophisticated 3-dimensional radiation planning computers or newer types of inherently more precise radiation.

Furthermore, the report called for the assessment in controlled trials of the role of postoperative radiation in patients with positive margins after radical prostatectomy. A large, randomized, NCI Cooperative Group trial of this approach was mounted in 1988 and will finally complete its accrual within the next year, though it will necessarily still take several more years to determine definitively whether this approach increases survival.

It was also suggested that researchers needed to assess in controlled trials the role of adjuvant hormonal therapy after prostatectomy and/or radiation therapy. Several large randomized Cooperative Group trials of adjuvant hormonal therapy--in various stages and with differences in timing of androgen deprivation and radiation--were launched and some have completed accrual. Preliminary outcomes indicate that freedom from prostate cancer progression is indeed improved, although there is no overall survival difference identifiable as yet. Newer studies are evaluating more prolonged therapy and the use of hormonal treatments prior to radiation or prostatectomy.

The conference report also asked researchers to clarify the clinical significance of extent of nodal involvement. We are able to report that, combined with serum PSA, nodal involvement is now clearly identified as indicative of poor prognosis in the absence of therapy. Randomized studies are under way that evaluate the modalities of pelvic radiation--to augment control of the disease regionally--and combined androgen blockade.

The report further suggested that researchers should develop instruments for assessing quality of life and psychological outcomes. Several appropriate instruments have been developed and validated, one of which--FACT-P--is now in wide usage. This type of quality of life analysis is now a routine aspect of major therapeutic trials whenever there is a potential significant difference. Moreover, quality of life and psychologic endpoints are a major emphasis area for the Community Clinical Oncology Program--CCOPs--which is participating in all the large randomized trials.

The final clinical research direction enumerated asked that researchers agree on a uniform clinical and pathologic definition of stage A1 prostate cancer. This issue has become moot as the rate of TURP has declined markedly and PSA surveillance has become common. Instead of the dilemma of subclassifying Jewitt stage A1, we have the 1990s dilemma of subclassifying TNM stage T1c: positive needle biopsy done for elevated PSA but without identifiable nodule. This is not entirely the same population of patients as A1 but is similar in that it must contain a

substantial cohort of clinically silent and unimportant cancer. Large series are being evaluated in an attempt to identify highly reliable molecular or other correlates of prognosis.

The first of the two basic research directions noted in the report asked that basic research be encouraged, to elucidate the fundamental processes of prostate cancer growth. This area has virtually exploded, along with similar developments that cut across the entire field of neoplasia. NCI has sponsored frequent workshops and conferences to bring together laboratory investigators working on prostate cancer. Fundamental and translational research has been further fostered by funding of prostate cancer--and other cancers--Specialized Program of Research Excellence--SPOREs--by NCI, and of Urology Research Centers by the National Institute of Diabetes and Digestive and Kidney Diseases--NIDDK. Examples of potentially dramatic discoveries in this field include: bcl-2 oncogene over expression in prostatic intra epithelial neoplasia (PIN); frequent loss of the E-cadherin gene on chromosome 16q22; unique mutations in the tumor suppressor gene p53; and the discovery of a new metastasis suppressor gene, KAI1, that is decreased in human cell lines derived from metastatic prostate cancers and has been mapped to human chromosome 11p11.2.

The second basic research direction called for assessment of the diagnostic and therapeutic role of prostate cancer-specific monoclonal antibodies. In general, unlabeled monoclonal antibody therapy has not proved unequivocally useful in other types of cancer, despite sometimes relatively specific tumor targeting. However, attempts to modify these antibodies by attaching toxins or radioisotopes are being investigated, as are techniques to combine monoclonal antibodies with recruitment of the more powerful cellular immune system.

In summary, a decade of research in prostate cancer has resulted in a great many significant findings with regard to causation, diagnosis, and treatment, in addition to the identification of new opportunities in both clinical and basic research as it relates to prostate cancer. Prostate cancer research has been, and will remain, a high priority within the NCI's research program.

PROSTATE CANCER FUNDING

Mr. Stokes: How much is included in the FY 1997 budget request for prostate cancer and how does this compare with funding level for FY 1996 and FY 1995?

Dr. Klausner: The NCI estimate for prostate cancer research in 1997 is \$72.2 million. This is an increase of 2% over the current 1996 estimate and a 10% increase over what was spent in 1995.

DECLINE IN BREAST CANCER MORTALITY RATES

Mr. Stokes: Last year, the committee heard considerable testimony from agency and public witnesses alike emphasizing the fact that the overall death rate for breast cancer in American women was declining. And, in fact, it had declined about 5 percent, between 1989 and 1992. To what extent is the decline expected to continue, and what progress do you have to report this year with respect to breast cancer?

Dr. Klausner: Breast cancer mortality trends for both black and white women in the United States have improved markedly in the 1990's compared to the 1980's. From 1989 to 1993, the most recent 5-year period of available data, the age-adjusted breast cancer mortality rate fell approximately six percent in white women and rose about one percent in African-American women. By comparison, from 1980 to 1989, the rate increased three percent in white women and sixteen percent in African-American women, according to data reported by the National Cancer Institute from the National Center for Health Statistics.

The overall rate in U.S. women has fallen 6 percent in recent years, dropping from 27.5 per 100,000 women in 1989 to 25.9 in 1993. This year an estimated 44,300 women will die of the disease nationwide, but that estimate could prove to be too high if the current trend continues. In both white and African-American women, the greatest improvements in mortality during the recent 5-year period were seen in younger age groups, but the changes were more modest in African-Americans than in whites of all ages. The available data would indicate a continued decline in breast cancer mortality for both white and African-American women.

Experts believe the recent decline in breast cancer mortality is partly a result of mammography screening, which rapidly increased in the U.S. during the 1980's and resulted in a shift toward the detection of breast cancer at earlier, more curable stages. But screening cannot explain all of the decline. Changes in mortality trends across a wide age range usually indicate improvements in medical intervention, and examination of stage-specific breast cancer incidence rates and survival rates suggests that both earlier detection and improved treatment are likely contributing to the recent declines in breast cancer mortality. The continued increase in breast cancer mortality in older women extends a long-standing, increasing trend in breast cancer risk for women born from 1900 to 1920. Researchers believe that the increasing mortality rates in this group reflect changes in risk factors such as childbearing patterns early in the century. Less well-understood is the declining mortality among women under age 40, which appears to reflect a recent change in risk factors above and beyond the improvements due to medical intervention.

Within the past 15 months, two major genes responsible for up to 90 percent of hereditary breast and ovarian cancers have been cloned BRCA1 and BRCA2. BRCA1, is a breast and ovarian cancer susceptibility gene on chromosome 17. In

high-risk families, women who carry mutations in BRCA1 have an 80-90 percent lifetime risk of breast cancer, and a 40-50 percent risk of ovarian cancer. Another breast cancer susceptibility gene, BRCA2, has been mapped to chromosome 13; mutations in this gene do not appear to increase risk of ovarian cancer.

Research is underway to define the predictive value of newly identified markers such as genes or gene products. We are finding that the absence or presence of certain proteins can indicate that a tumor is more likely to recur or to be more aggressive. Learning to read these molecular signs will enable us to tailor treatments to individuals. For example, women whose breast cancers express high levels of the oncogene c-erbB-2 appear to experience more aggressive tumor development, and higher treatment intensity may be more effective than low intensity treatment.

NCI continues to support research to develop imaging technologies with greater sensitivity and specificity than conventional mammography such as digital mammography, computer-aided diagnosis, magnetic resonance imaging, nuclear medicine, digital ultrasound, PET imaging, and optical imaging. Studies suggest that the chance of cure for women with advanced breast cancer or with adverse prognostic indicators may be increased by a higher dose of chemotherapy, but this may be toxic to the patient's bone marrow, thereby increasing the likelihood of infections. Autologous bone marrow transplantation (ABMT) can reduce this complication. NCI is sponsoring randomized clinical trials to determine if high-dose chemotherapy with ABMT increases survival in women with advanced or poor prognosis breast cancer. Validating promising breast cancer therapies in clinical trials is a high priority for NCI. When a trend becomes apparent in these trials, NCI advises investigators and physicians to modify or stop their trials or treatment regimens.

The United States Postal Service will issue a Breast Cancer Awareness Stamp on June 15. NCI's CIS toll-free number will appear on the border of each sheet of stamps as the source for breast cancer information. In addition, educational materials will be available at post offices across the country, and a video on breast cancer produced by LIFETIME television will be shown in more than 2,000 post office lobbies. NCI helped develop resources and media products for the information campaign. ENCORE^{plus}, a program of the YWCA of the U.S.A., the American Cancer Society, and several breast cancer groups will join with the Postal Service to provide breast health information forums and mammography screenings at selected post offices and other community locations.

Research in other parts of the United States may help clarify the genetic, hormonal, and/or environmental influences on breast cancer. In collaboration with the National Institute of Environmental Health Sciences, NCI is conducting the Long Island Breast Cancer Study Project (LIBCSP) to evaluate the contribution of various environmental and occupational factors to the etiology of breast cancer, and to develop a geographic system to evaluate current and past exposures. Current projects funded at New York area universities and cancer centers are studying a

variety of compounds including organochlorines, polycyclic aromatic hydrocarbons, estrogen metabolites, genetic factors, and electromagnetic field (EMF) exposures, and are collecting tissue samples and data about family history to elucidate connections between environmental factors and breast cancer. The Northeast/Mid-Atlantic Study is examining the role of various environmental exposures along with other possible risk factors to better understand the causes of breast cancer in the northeastern United States, an area of high incidence and mortality.

INTERCULTURAL CANCER COUNCIL

Mr. Stokes: Are you familiar with the intercultural cancer council, and if so, in what ways are you working with the council to ensure that cancer in minority groups is addressed by NCI research?

Dr. Klausner: The NCI has been working with the Intercultural Cancer Council--ICC--in a number of ways. First, an NCI conference grant helped support a national meeting last year focusing on minority cancer research coordinated by the ICC. Second, and most importantly, the ICC now has a liaison representative to the National Cancer Advisory Board. In addition, a number of members of the ICC participate on a number of NCI advisory boards including the Board of Scientific Advisors. The NCI has also solicited input from the ICC regarding membership on several Program Review Groups including the Prevention Trials Review Groups, the Cancer Centers Review Group, the Cancer Control Review Group, the Developmental Therapeutics Review Group and the Behavioral Research Review Group.

Through ICC's Washington, D.C. offices, NCI activities of interest have been publicized and include two Request for Applications--RFAs--"Women and Minority Recruitment: Intervention Testing," and "Women and Minority Recruitment: Small Grants Program." Through NCI's Comprehensive Minority Biomedical Program (CMBP), support is given to newly trained minority clinicians to acquire training and research experience in clinical oncology and to increase minority representation in clinical oncology.

CANCER VACCINES

Mr. Stokes: What progress do you have to report to the committee this year with respect to designer therapies, tumor specific therapies and antibodies that can carry a therapy right to the cancer cell? I would think that this advance has major implications for improving that treatment of other diseases as well.

Dr. Klausner: A large number of cancer vaccines have been introduced into the clinic over the past 3-5 years. The basis for this expanded clinical research in cancer vaccines is related to several factors including a greater understanding of elements important in the anti-cancer immune response--for example, the recognition of the critical role that T lymphocytes play in the anti-tumor immune response; an explosive growth in the understanding of antigen presentation and T-cell activation;

the ease with which genes can be introduced into cancer cells to modulate their immunogenicity; and advances in immunology and molecular biology that have allowed both the identification of new cancer-specific antigen targets, and the construction of defined antigen vaccines. Counted among these new T-cell antigen targets are the many tumor-specific or tumor-associated proteins involved in neoplastic transformation and progression, such as mutated oncogenes, viral transforming proteins, or over expressed normal proteins involved in growth factor receptor-ligand interactions or cell signaling, as well as proteins involved in the differentiation of the tissue from which the tumor cell is derived. In addition, several vaccines that induce antibody rather than T-cell responses are being developed against antigens that are over expressed in several malignancies, for example, melanoma, or adenocarcinomas of the breast, ovary or colon.

Substantial preclinical and clinical efforts are being devoted to optimizing methods of presenting tumor antigens to the immune system that will result in potent antitumor immune responses. Because in many cases the tumor antigens are not yet known or are unique to the patient's own tumor, attempts are being made to immunize patients with their own tumor cells, modified by insertion of new genes that increase the immunogenicity of the tumor antigens within the cell. These genes include cytokines or T-cell costimulatory signals that call in the body's professional antigen-presenting cells to the vaccine site, or allow tumor cells to directly present the tumor antigen to T-cells. In addition to vaccines composed of whole autologous tumor cells, investigators have recently initiated studies of vaccines composed of purified fractions of the patient's own tumor--for example, heat shock proteins, or lymphoma/myeloma idiotypes.

In the increasingly more common setting where a tumor antigen has been identified and cloned and is known to be shared between patients, several techniques of immunization are being evaluated in the clinic to determine which might induce the most potent immune responses. For example, the DNA for the gene encoding the antigen can be injected directly into the patient; or it can be inserted into several viruses or bacteria that carry the antigen gene directly into the cells--professional antigen-presenting cells--responsible for stimulating immune responses in the patient. Alternatively, the protein antigen or the peptide epitopes--the actual pieces of the protein that are recognized by the immune system--can be produced by synthetic or recombinant means, and then administered to the patient with non-specific immunologic adjuvants or 'loaded' onto or into the cells.

While recently-published randomized surgical adjuvant studies in melanoma and colon cancer with older vaccines--autologous tumor in colon and vaccinia oncolysates in melanoma--were disappointing, showing no effect of the vaccines on survival, some historically-controlled series of the older vaccines, studied in melanoma patients--both in advanced disease and the surgical adjuvant setting--suggest that the vaccines are having therapeutic effects. These results must be confirmed in larger randomized trials which are only now beginning. The newer vaccines--gene-modified autologous cancer cells and defined antigen vaccines--are in the earliest phase of testing and some are being considered for randomized trials.

Although in several of the clinical trials the cancer vaccine is clearly inducing antigen-specific immune responses in patients, and occasional patients with advanced disease have had tumor shrinkage in response to immunization, it is likely that 2-3 years of additional testing in pilot studies will be needed to optimize the vaccine-induced immune responses sufficient to consider moving forward with more definitive large scale testing in randomized studies. Furthermore, intensive research is now beginning to develop interventions that reverse or bypass possible mechanisms used by tumor cells to escape immune detection.

In the field of antibody and immunotoxin research, the results of antibody clinical trials had been largely disappointing, despite their initial promise. This is due to a variety of reasons, including the heterogeneity of the tumor--that is, the capacity of tumors to lose the antigen recognized by the antibody; the development of immune responses against the foreign portion of the antibodies, most of which were produced in mice, limiting treatment to just one course; the difficulty of the antibody in penetrating into the tumor masses; and perhaps the weak killing potential of the antibodies. Several developments in the past few years suggest that these obstacles can be overcome, and there are now promising data that antibody-directed therapy can produce clinical benefit with minimal toxicity in at least some clinical situations.

In addition to these methods, several non-immunologic approaches to direct targeting of cancer cells are being explored in the preclinical and clinical settings. Recent preclinical data suggest that, in the near future, vectors--the delivery vehicles for the gene of interest--will become available that can deliver genes specifically to the intended target cells, by manipulating the vectors to recognize receptors expressed only or predominantly on the target cells. Once inside the cell, expression of the therapeutic gene can also be controlled by driving the expression of the gene with a promoter that is active only in the target cells. For example, the tyrosinase gene is expressed only in melanocytes--normal pigmented cells--and melanoma. A gene introduced into cells whose transcription is driven by a tyrosinase promoter will be expressed only in melanocytes or melanoma.

Another example of a tumor-specific therapy is an adenovirus engineered to replicate and kill the cells it infects, only if the infected cells do not have a functioning p53 gene. Since normal cells have a normal p53 gene, but many cancer cells do not, this adenovirus can be injected locally into a cancer and will replicate only in the cancer cells, leading to selective killing of the cancer cell, but not normal surrounding cells. Clinical trials of this adenovirus construct will be initiated in the near future.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are underway, and what are we expected to learn from them?

Dr. Klausner: A critical component of the National Cancer Program is NCI's clinical trials program. This includes a comprehensive structure of clinical trials in treatment, early detection, and prevention. The major components of the program include the cancer centers and the cooperative groups plus our intramural research effort. The Community Clinical Oncology Program is also a crucial component, extending the opportunity for participation in clinical trials to communities across the country.

The nationwide cooperative groups program promotes and supports clinical trials in cancer prevention, early detection, treatment, and rehabilitation. More than 1,400 institutions and 9,000 investigators participate in these cooperative group studies. The sheer number of different types of cancers and the biological complexity of individual cancers present extraordinary challenges to the efficient clinical investigation of new anti-cancer agents or new treatment strategies suggested by laboratory and animal experiments. To more rapidly test such potential treatment advances in patients, the NCI maintains a standing funded clinical trials program to conduct such investigations. In this way, new clinical trial organizations do not have to be created each time a potential new cancer treatment emerges. Nine NCI-sponsored Cooperative Groups place approximately 20,000 new patients onto cancer treatment protocols annually, principally large randomized Phase III clinical trials that have been responsible for establishing the current state of-the-art for cancer treatment worldwide.

In addition, new anti-cancer agents being studied for the first time in patients are entered into Phase I and Phase II clinical trials; many of these early treatment clinical trials are conducted under NCI Investigational New Drug (IND) sponsorship in institutions funded by NCI cooperative agreement grants. Currently, over 200 investigational agents or treatment strategies, ranging from new chemotherapy drugs and cancer vaccines to agents that prevent tumor blood vessel development, are being studied under NCI INDs. Many of these agents are being developed clinically as a result of active NCI cooperation with biotechnology and pharmaceutical companies, accelerating the clinical testing of scientific advances emerging from these sources. Others come from the scientific laboratories and discovery programs of the NCI itself. Examples of important new anti-cancer agents that have recently come from NCI development include paclitaxel (Taxol®) for ovarian and breast cancers, interferon alpha for malignant melanoma and chronic myelocytic leukemia, fludarabine for chronic lymphocytic leukemia, and trans-retinoic acid for acute promyelocytic leukemia.

Science is increasingly delineating the distinct biological bases for many tumors. As a result, many clinical trials of new treatments are linked to particular laboratory studies, and many NCI trials now include laboratory components in addition to the clinical evaluations. For example, clinical studies of new acute leukemia treatments now routinely include the analysis of genetic changes in the malignant leukemia cells of the individual patient. The NCI has funded small clinical trials groups especially to evaluate potential new treatments for patients with

brain tumors, malignancies occurring in the setting of AIDS, and pediatric tumors, due to the very specialized nature of these cancers. A similar program has very recently been established to develop new therapies for breast cancer. Furthermore, recognition of gender, age-related, and ethnic differences in individual responses to cancer therapy has led to initiatives to make such evaluations a routine part of the clinical development of new anti-cancer agents. A recent NCI evaluation shows that minority populations participate in treatment clinical trials in proportion to their cancer risk. Minority participation in clinical research is a high priority for the Institute.

Greater patient access to advanced therapeutic approaches has been a chief goal of the NCI clinical trials program. The field of childhood cancers is a success in this regard. More than 90 percent of children who develop cancer in the United States annually are treated at institutions participating in the NCI-sponsored pediatric Cooperative Groups. While the percentage of adults with tumors treated on protocols is much smaller - on the order of three percent, more than 8,500 oncologists participate in NCI trials, allowing patients to benefit from advanced treatment approaches whether they are seen at the most comprehensive cancer center or the smallest community hospital.

The CCOP program is a mechanism that links community cancer specialists and primary care physicians with clinical Cooperative Groups and cancer centers to conduct cancer treatment, prevention, and control clinical trials. Currently, there are 52 CCOPs in 30 states, with 300 participating hospitals where approximately 3,000 physicians cooperate to enter patients and individuals at risk for cancer on NCI-approved clinical trials. An additional 10 minority-based CCOPs are funded to enhance the participation of minority populations in clinical trials research. These programs are located in nine states and Puerto Rico, bringing an additional 42 hospitals and 350 physicians into the clinical trials network. Through this network, individuals can access state-of-the-art clinical research trials while remaining in their home communities.

Each year the CCOPs enter about 4,000 patients into cancer treatment clinical trials - accounting for about one-third of all patients on NCI treatment efficacy trials. An additional 4,000 participants are entered onto cancer prevention and control clinical trials from the CCOP communities. Support is also provided for university members and affiliates to participate in prevention and control research.

The current CCOP program covers the spectrum from testing new combinations of anti-tumor drugs in cancer patients to providing healthy men and women with agents for the purpose of preventing first occurrences of cancer. Examples of the latter are the Breast Cancer Prevention Trial and the Prostate Cancer Prevention Trial. CCOPs have also demonstrated successful interventions for symptom management and continuing care of cancer patients, including treatment for mucositis and hot flashes, common side effects of chemotherapy. The program is rapidly evolving to include interventions for individuals with specific molecular alterations associated with genetic cancer susceptibilities.

Linking the community, university researchers, and the NCI, the CCOPs have proven to be one of the critical paths for the dissemination of state-of-the-art cancer treatment information. The CCOP research network is well positioned to conduct the research of the future that will move oncologic practice from the treatment of established disease to the management of cancer risk.

Among the most significant clinical trials underway are the Breast Cancer Prevention Trial (BCPT) with tamoxifen and the Prostate Cancer Prevention Trial (PCPT) with finasteride. The results of these two studies may lead to an ability to prevent breast cancer and prostate cancer.

The BCPT is a randomized clinical trial that is testing the effectiveness of tamoxifen for preventing breast cancer. Since June 1992, twelve thousand women at increased risk of developing breast cancer, based on factors such as age, family history, and personal history, have entered the study. Twenty percent of BCPT participants have two or more first-degree relatives - mothers, sisters, daughters - with a history of breast cancer, thus providing a unique resource for understanding breast cancer genetics. The average relative risk for BCPT participants is about five times as great as that for a comparable group of individuals in the general population. If proven effective, tamoxifen could provide an option to prevent breast cancer in certain women at high risk of developing the disease. Each woman participating in the BCPT is scheduled to take tamoxifen or placebo for five years.

The PCPT is a randomized clinical trial involving 18,000 healthy men over age 55. Started in 1993, and anticipated to yield definitive answers within 10 years of initiation, the PCPT will determine if the drug finasteride can prevent prostate cancer. The PCPT may also help to better define who is at risk for clinically significant prostate cancer and to improve early detection and prostate cancer screening technologies. So far, over 16,000 men have entered the PCPT which is expected to complete the enrollment phase by the end of calendar year, 1996.

The Prostate, Lung, Colorectal and Ovarian Cancers Screening Trial (PLCO) for men and women began accrual in November 1993 and is planned to continue for 16 years. Some 37,000 men will be screened for 4 years for prostate, lung and colorectal cancers and 37,000 women will be screened for the same period for lung, colorectal and ovarian cancers. Equal numbers of men and women are being followed with routine medical care as controls. There will be a ten year follow-up study of both subjects and controls to determine the effects of screening for those four sites on mortality.

The Polyp Prevention Trial is a trial testing the effect of dietary intervention in individuals with prior colonic polyp removal. Half of the patients enrolled in the trial are allocated a dietary counseling program aimed at reducing their intake of fat and increasing their intake of fruits, vegetables and fiber. The other half are allocated standard management. The study will question whether dietary change will reduce the recurrence rate of adenomatous polyps.

The Colon Cancer Prevention Trial is evaluation aspirin, or ASA, as a preventive intervention in patients with completely resected early stage colon cancer and in Stage B2 and C patients with no evidence of disease after 5 years. This double-blind, placebo-controlled trial of ASA will measure reduction in new adenoma formation. The study will also assess whether ASA will increase disease-free survival in patients diagnosed with colon cancer. Calcium carbonate is also being evaluated as an alternative to aspirin for colon adenoma prevention.

A large scale intervention trial is being initiated which will assess the effectiveness of *Helicobacter pylori* antibiotic therapy and supplementation with vitamin-mineral and garlic preparation in inhibiting or reversing the progression of precancerous gastric lesions in Chinese persons.

A randomized, controlled clinical trial has been designed to define the criteria that will discriminate those women with atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL) who are at high risk of developing invasive cervical cancer. The vast majority of these lesions will not progress to cancer; however, the proper treatment of these lesions requires continuing evaluation, as well as the development of new triage techniques. In addition recent studies have established that most women with cervical dysplasia-neoplasia have HPV DNA associated with those lesions. The clinical trial will determine whether oncogenic HPV strains can be used in the context of ASCUS and LSIL in order to accurately predict the diagnostic accuracy and natural history of these histologically low-grade lesions.

The Autologous Bone Marrow Transplant (ABMT) trial examines breast cancer patients in which both peripheral blood and bone marrow stem cells are genetically altered with the multi-drug resistant gene *mdr1*. Patients are given high dose Chemotherapy prior to the ABMT. They are then treated with Taxol[®], and the presence of the *mdr1* transduced hematopoietic cells is assessed. Currently, there are two patients undergoing this treatment.

Another trial is investigating whether patients can be reconstituted with *mdr1* gene marked cells following treatment with nonablative chemotherapy. This has implications to the general oncology community - since it asks the question whether gene therapy is useful in patients not undergoing a transplant.

The trial, Protocol 94-C-0031, is determining whether cellular or humoral immunity specific to an individual patient's tumor mutant *ras* or *p53* oncogene products exists. The trial also examines whether the immunity can be induced or boosted by vaccination with a synthetic peptide and assess the tumor's response to the vaccination.

Two trials currently underway are evaluating the clinical response and toxicity following multiple dose administration of humanized anti-Tac monoclonal antibody conjugated with Yttrium-90 in patients with Tac-expressing adult T-cell leukemia (ATL) and in patients with Tac-expressing T-cell malignancies other than ATL.

Protease inhibitors are drugs belonging to a new class of therapeutic agents. They inhibit the formation of viable virus particles and are therefore powerful weapons in the fight against HIV infection. Both Indinavir and Ritonavir have been approved by the FDA in March 1996 for the treatment of HIV-infected adults and children over the age of 13 years. The National Cancer Institute is conducting the only studies in children with these two drugs and we hope to have enough data later this year to apply to the FDA for approval of these drugs for the use in children. We have so far enrolled 45 and 30 children, respectively, into these two studies. Both protease inhibitors appear to be well tolerated and show promising activity against HIV, as measured by a decrease in the amount of circulating virus and increase in the number of CD4 cells, the main components of a healthy immune system. These studies will not only give us insight into the correct dosing of these new drugs when used in children but will hopefully also help to answer some important questions about the changes in viral load during a single day and over time as well as to what kind of mechanism the immune system employs to repair damage and produce new cells. This will have impact not only on the understanding and treatment of HIV disease in children and adults but may also further our knowledge in regard to repair mechanisms in other Immunocompromised patients.

Some of the most interesting and important treatment clinical trials that are currently being funded from the clinical group mechanism are as follows:

BREAST CANCER

INT 0121 - A study of conventional adjuvant therapy vs. conventional adjuvant chemotherapy followed by high dose chemo and autologous bone marrow transplant (ABMT) as adjuvant intensification therapy in patients with stage II and III breast cancer with > 10 positive axillary nodes: is intensification beneficial?

The Significance - This study tests standard adjuvant chemotherapy against the same standard therapy plus intensification requiring high dose chemotherapy and stem cell support. The latter strategy is increasingly being advocated but has significant costs in terms of toxicity and expense. Taken in tandem with CALGB 9082 (see below), this study should reliably define the role of ABMT in adjuvant chemotherapy for this group of patients.

CALGB 9082 - A randomized, comparative study of high dose cyclophosphamide, cisplatin and BCNU (CPA/CDDP/BCNU) and ABMT versus standard dose CPA/CDDP/BCNU as consolidation to adjuvant CAF for patients with operable stage II or III breast cancer involving > 10 axillary nodes: is intensification beneficial?

Significance - All patients on this study receive standard adjuvant chemotherapy induction with CAF and then are randomized to high dose chemo with stem cell support or the same chemo at intermediate doses with G-CSF support. The phase II results of the experimental high dose arm (CALGB 8782- Proc.ASCO 11:58,1992) were recently updated and show a 5 yr DFS rate of 71%. Taken in tandem with INT 0121, this study should reliably define the role of ABMT in adjuvant therapy in this clinical setting.

S9623 - A comparison of intensive sequential chemotherapy using doxorubicin plus paclitaxel (Taxol®) plus cyclophosphamide with high dose chemotherapy and autologous hematopoietic progenitor cell support for primary breast cancer in women with 4-9 involved axillary nodes

Significance - This study compares two aggressive but different approaches to high dose chemotherapy. The study will accrue 1000 patients (500 per arm) and should definitively answer whether a stem cell supported, inpatient regimen is better than an aggressive, outpatient G-CSF supported regimen in this cohort of women with breast cancer.

INT 0148 - Is there a benefit from doxorubicin dose escalation, with or without Taxol®, as part of the adriamycin/cyclophosphamide (AC) adjuvant chemotherapy regimen for node positive breast cancer; is there benefit from adding Taxol® to AC?

Significance - This study is sufficiently powered (accrual = 3000 patients) to answer two important questions: (1) Is there a dose-response relationship for doxorubicin in the clinically tolerable dose range? (2) Does taxol add to standard adjuvant AC chemotherapy when administered in a sequential fashion? Important supplementary questions regarding c-erbB-2, % S phase, topoisomerase II levels and their role in predicting response to high dose chemotherapy will be evaluated.

NSABP B-27 - Does taxotere added to preoperative AC chemotherapy benefit patients with operable breast cancer? Is it preferable to add taxotere prior to or after surgery?

Significance - This is the first study to introduce the potent new taxane, taxotere, into the adjuvant setting. This study is a follow-up to NSABP B-18 and asks whether the subset of patients with node positive disease following neoadjuvant chemotherapy benefit from additional post-operative adjuvant therapy. This neoadjuvant approach facilitates the evaluation of tumor markers pre- and post-treatment. This treatment model will allow the study of mechanisms of drug resistance and the exploration of changes in several important oncogene products (p53, nm23, and c-erbB-2).

COLORECTAL CANCER

INT-014 - Can minimally-invasive laparoscopic colectomy be safely substituted for open colectomy for resectable colon cancer?

Significance - As for several other solid tumors, the possibility of decreasing operative morbidity and improving overall quality of life with refined and less invasive surgical approaches is now being examined for colon cancer patients. In the US, less invasive surgery in the form of laparoscopic colectomy has become fairly widely available. However, it is not yet clear whether this technique is fully equivalent to standard open colectomy in terms of efficacy and safety.

This randomized Intergroup trial represents a collaborative effort among selected institutions in 5 Cooperative Groups to compare laparoscopic colectomy with standard colectomy as potentially curative therapy for patients with operable - Stage A through C, non-metastatic colon cancer, excluding those patients in whom the creation of a colostomy is deemed necessary. The trial employs endpoints of disease-free and overall survival, patterns of disease recurrence, the need for more extensive surgery at the time of the initial operation in those randomized to laparoscopy, overall costs of medical care and quality of life. Many of the patients enrolled in the laparoscopic colectomy study will also be participating in randomized surgical adjuvant chemotherapy studies, as appropriate to their disease stage.

INT 0136 - Can peri-operative 7-day infusion of adjuvant chemotherapy further improve survival when added to standard post-operative adjuvant therapy for resectable colon cancer?

Significance - This trial builds on the unexpected final result of a prior randomized trial, NSABP C-02, a study of portal vein infusion of 5-FU during the immediate post-operative, or "peri-operative", period. Surprisingly, although that trial had been designed to address a locoregional control question, it demonstrated improved systemic control and resultant freedom from distant disease progression. It is hypothesized that this benefit was related either to the immediate post-operative chemotherapy timing, or to the use of continuous infusion.

An Intergroup randomized trial for Dukes' C colon carcinomas is therefore testing intravenous, instead of portal vein, infusion of chemotherapy for the first seven post-operative days, in addition to conventional systemic adjuvant therapy as appropriate for disease stage. In addition, INT-0136 is investigating prospectively allelic deletions of 17p12 (p53) and 18q21 (DCC) in relation to prognosis and response to adjuvant therapy. ECOG investigators have recently demonstrated 18q deletions appear to discriminate between good- and poor-risk subgroups of patients with T3 (Dukes' B2) tumors.

INT 0153 (colon), INT 0144 (rectal) - Will protracted venous infusion (PVI) of 5-FU-based chemotherapy be superior to bolus 5-FU regimens in adjuvant therapy of resectable colon and rectal cancers?

Significance - Both these studies derive from another unexpected but unequivocal positive result from a completed large Intergroup trial in rectal cancer. That study - NCCTG 86-47-51 - had a factorial design that randomized between 5-FU $\pm$ MeCCNU and between 5-FU by bolus or 5-FU by PVI as a "radiosensitizer" during the RT phase of treatment. MeCCNU added nothing but toxicity. On the other hand, even with relatively brief follow-up thus far, PVI - as opposed to bolus 5-FU - given during RT, was associated with improvements in both disease-free survival - 67 percent vs. 56 percent - and, to a lesser degree, overall survival - 76 percent vs. 68 percent, demonstrating that PVI exerted both local and systemic effects. Importantly, the impact of PVI was measurable even though only one of the chemotherapy cycles - the cycle concurrent with RT - was given by PVI. That study not only serves as the basis for the current trials but also further validates the role of adjuvant chemotherapy in rectal cancer.

INT-0144, therefore, was developed for rectal cancer patients who are not referred pre-operatively and thus not eligible for the neoadjuvant - pre-op versus post-op - studies described below. INT-0144 is testing PVI 5-FU more definitively by applying PVI during all phases of therapy in one arm of the study and will further explore the effects of bolus 5-FU prior to and following RT, with the aim of defining a strategy that provides further prolongation and quality of survival over previous studies. The three arms of this post-op adjuvant rectal cancer Intergroup chemoradiation trial are: arm 1- PVI 5-FU in all phases; arm 2- PVI only during RT - the best arm of the completed intergroup study N86-47-51; arm 3- 5-FU/leucovorin/levamisole - with bolus 5-FU/leucovorin during RT. The control arm was the most aggressive arm of the previous generation of Intergroup studies, with the original assumption that the triplet regimen would prove to be either superior to, or no less effective than, the doublet regimens of 5-FU plus either levamisole or leucovorin. INT-0153, coordinated by SWOG, is similarly studying PVI 5-FU + levamisole in colon cancer and comparing to the empirically chosen control arm of the triplet 5-FU/leucovorin/levamisole regimen. Because of the recent trial results to be reported at ASCO in May, the triplet regimen in both of these studies is being modified so that they will utilize only doublet therapy as a control in newly entered patients.

NSABP R-03, INT 0147 - Will pre-operative (neoadjuvant) chemoradiation be superior to entirely post-operative adjuvant chemoradiation in operable rectal cancers?

Significance - In several other solid tumors including breast cancer, and in the management of bulky rectal cancers that are not initially resectable, there is evidence to suggest the superiority of neoadjuvant timing of chemotherapy or chemoradiation. In rectal cancer such an approach has led to durable freedom from recurrence in initially inoperable cases. In addition, even operable rectal cancer involves a compromise type of surgery with poor exposure and extremely limited surgical margins, and of course frequently requires permanent colostomy with its attendant morbidity.

The possibility of using neoadjuvant chemoradiation to improve current results has led to two separate large phase III randomized trials of preoperative vs postoperative combined modality therapy for resectable rectal cancer - INT-0147 and NSABP R-03. These are evaluating the role of neoadjuvant pre-operative chemoradiation in improving disease-free and overall survival and in reducing the proportion of patients who require a permanent colostomy. In both studies, combined chemoradiation is given either before surgery or after, with the total dosage of both chemotherapy and radiation being identical between arms. The neoadjuvant approach is being compared to the conventional sequence of adjuvant post-operative chemoradiation for high-risk rectal cancers.

INT C9581 - a) Can immunotherapy with MoAb 17-1A improve survival in the generally low-risk setting of Dukes' B2 colon cancer; and b) Can molecular and other markers identify patients within Dukes' stage B2 with different prognoses with and without therapy?

Significance - One lead for new surgical adjuvant trials in colon cancer derives from a recent report from Riethmüller et al. of a German multicenter trial that entered 189 patients with colon (58%) or rectum (42%) high-risk tumors randomized to receive either no additional therapy or a postoperative infusion of 500mg of 17-1A antibody plus 4 further infusions of 100mg at one-month intervals. 17-1A is a murine monoclonal IgG2a antiepithelial antibody generated in 1979 by Koprowski. It reacts with 17-1A antigen, which is a 37-40 kDa transmembrane glycoprotein expressed in fetal tissue and on normal and malignant epithelial cells, particularly differentiated colorectal carcinomas. The function of 17-1A is unclear but it may be involved in cell to cell adhesion. The median follow-up on this trial at the time of the report was 5 years. Riethmüller et al. reported about a 30% decrease in mortality and a 27% reduction in recurrences. There was no apparent effect on local recurrence; the difference appeared to be confined to the rate of distant metastases. The magnitude of the apparent benefit would seem to suggest rough equivalence to the kind of benefit identified previously for adjuvant chemotherapy. There was no obvious difference between colon and rectal primary sites. In the German trial, no chemotherapy was utilized, an approach that ignores the confirmed evidence of benefit from adjuvant chemotherapy in prior US Intergroup studies. However, in the U.S. current Intergroup adjuvant trials have excluded patients with Dukes B2 disease, a subgroup where the benefit of chemotherapy has been difficult to demonstrate because the event/recurrence rate is smaller, though by no means negligible.

These patients are an excellent focus for study of a minimally toxic, limited duration immunologically based therapy and all the Cooperative Groups have been interested in confirming or refuting the German experience with MoAb 17-1A in this setting. Furthermore, the other major goal of the trial will be to test prospectively whether tumor cell ploidy, allelic loss of chromosome 18q, expression of thymidylate synthase, or other biomarkers can be used to stratify risk for Dukes' B2 patients and thus make trials both more efficient and more appropriate in this subgroup.

PROSTATE CANCER

T94-0131/PIVOT - Can radical prostatectomy for prostate cancer be demonstrated to improve overall survival for operable patients below the age of 70, and if so are there predictors for this benefit?

Significance - Some of the most fundamental issues in management of prostate cancers have been established in clinical practice without ever having been fully investigated in appropriate randomized trials. The most challenging recent study to develop, and potentially one of the most important, has been the NCI-VA Prostate cancer Intervention Versus Observation Trial of radical prostatectomy versus watchful waiting and conservative management. When first presented, this study was widely felt to be critically important but impossible to do because of patient and physician biases, the complex nature of the issues required for truly informed consent, and other logistical issues.

The mechanisms that have been brought to bear to overcome these hurdles have included recruiting large numbers of centers - so that few patients will be required in each, collaboration between the NCI and the VA system, production of sophisticated video patient education materials - partly supported by AHCPR, and intensive lobbying within the Group GU committees and at other national urology meetings. This trial opened in the VA system and then in three NCI Cooperative Groups in FY95. There are about 30 NCI-sponsored performance sites, as well as 45 others in the VA system. The study was recently designated as an NCI High Priority Trial.

There are several unusual aspects to this trial, not the least of which is that parallel survival data will be collected on each site's patients contemporaneously eligible for randomization on PIVOT but refusing randomization. This will ultimately allow an assessment of how the randomized population may differ from an unselected population, and whether the results of the two approaches, radical prostatectomy vs observation, yield different results in other settings.

INT/NCCTG Radiation versus Observation (RIVOT) - Can radical radiation therapy for localized prostate cancer be demonstrated to improve overall survival, and if so are there predictors for this benefit?

Significance - The role of radiation therapy (RT) for clinically localized disease is barely more firmly grounded in randomized clinical trials data than the role of prostatectomy. However, since many of the VA hospitals do not have their own radiation facilities, and since a 3-way randomization was felt to be too difficult for patients and their physicians, the PIVOT trial does not address radiation.

For this reason, CTEP has promoted the development of a parallel phase III Intergroup Radiation vs. Observation Trial for early prostate cancer, with a general design similar to PIVOT, randomizing between RT and watchful waiting. Like the PIVOT trial, this parallel trial will require significant Intergroup resources necessary to draw on a requisite large pool of patients.

INT 0086 - Does adjuvant radiation improve survival and/or morbidity from local recurrence in patients with pathologic stage C (extracapsular) prostate cancer after radical prostatectomy?

Significance - Recent data based on PSA evidence of progression have shown that such patients have 30-50 percent PSA failure within 3 years following prostatectomy. An Intergroup trial led by SWOG is evaluating adjuvant RT in pathologic Stage C prostate cancer by randomizing post-prostatectomy patients to either receive RT or not.

This important national High-Priority trial has accrued very slowly because the patient's decision to volunteer for randomization is a particularly difficult one; most patients accepted radical prostatectomy and its sequelae with the hope of cure and the tacit presumption that surgery represented a more definitive option than RT. Moreover, with the marked increase in prostatectomies, the cohort of pathologic Stage C patients is increasing and RT has frequently been utilized despite the absence of previous data to confirm that RT may provide some chance of cure in this situation. This trial has therefore been given the highest priority in the Cooperative Group system for this stage of disease.

RTOG 94-12 - Are there important racial and socioeconomic differences in pre-treatment serum PSA levels, and do these correlate with prognosis or differential response to therapy of prostate cancer?

Significance - The marked differences in prostate cancer incidence and stage distribution by race and ethnicity are widely recognized but poorly understood. As well as whatever insights into prostate cancer biology may be gleaned from exploration of this problem, the answers may be of great relevance to the design, analysis and generalizability of therapeutic clinical trials.

Since RTOG has had a good track record of accruing minorities to its rapidly accruing large prostate cancer trials, this represents an opportunity to analyze for factors other than disease stage that may govern some of the apparent racial differences in PSA and/or behavior of the disease.

INT 0105 - Does flutamide augment the initial endocrine therapy - by orchiectomy in this trial - of advanced prostate cancer?

Significance - Very substantial controversy continues, despite many trials and a recent meta-analysis, as to whether combined endocrine therapy offers any meaningful advantage over simple medical or surgical castration, and if so, for

which subgroups of patients. The first major Intergroup trial showed that total androgen blockade (TAB) with an LHRH analogue and flutamide was not superior overall to LHRH alone, but in the most favorable cohort (with presumably the smallest proportion of androgen-independent cancer) TAB was superior in terms of DFS, QoL, and OS. However, numerous other trials of roughly similar design have provided conflicting, or at least nonconfirmatory, results. The recently published meta-analysis concluded that QoL was improved by TAB, but not OS.

This comparison of bilateral orchiectomy with or without flutamide for the treatment of patients with histologically confirmed stage D1 or D2 prostate cancer, which will be analyzed imminently, should help resolve this controversy by virtue of its design, its large size, and its prospective selection of the subsets to be analyzed with adequate power.

INT C9480, INT E8892 - What is the role for suramin chemotherapy in advanced prostate cancer, either androgen independent or "early" - that is, when still likely to be androgen dependent?

Significance - Suramin was developed and first tested for hormone refractory disease at NCI. Subsequent trials have refined its use and modified its initially daunting clinical toxicity profile. However, it is as yet not clear whether all the clinical effects previously attributed to suramin are related to its interesting mechanisms of action - such as inhibition of growth factor binding and antiangiogenesis, its profound adrenal suppression, to the simultaneous imposition of other endocrine manipulations, etc. Moreover, in what circumstances the potential benefits outweigh the complexity and side effects of therapy remain to be determined. The sequence of studies described below will begin to dissect these issues and - it is hoped - resolve some of the most perplexing questions about the importance of suramin as an antitumor agent. Parke-Davis' registration trial compares suramin + hydrocortisone to placebo + hydrocortisone and focuses on relief of pain in patients with hormone refractory disease. Now that this trial is nearing completion, Intergroup investigators will address the very problematic dose-response relationship by comparing three dose levels and targeting objective parameters of response, plus toxicity endpoints. Perhaps the most interesting ultimately is the Intergroup randomized trial for a cohort of higher-risk advanced but hormone-naïve - not hormone refractory - patients, because it may afford the best opportunity to ascertain whether suramin can have an impact on survival. This trial will assess the addition of suramin to the presumptive best available hormonal therapy, combined medical or surgical castration plus flutamide. A simplified suramin dosing scheme not requiring adaptive control is used in all these studies, and the combination including flutamide has been piloted in the Cooperative Groups.

PEDIATRIC ONCOLOGY

CCG 3891 - Conventional dose chemoradiotherapy versus ablative chemoradiotherapy requiring autologous bone marrow transplantation (ABMT) for high risk neuroblastoma: does ablative chemotherapy improve outcome?

Significance - The primary objective of the CCG-3891 protocol is to determine whether myeloablative therapy with ABMT is superior to conventional chemotherapy for children with neuroblastoma. Following induction chemotherapy, patients are randomized to either continue receiving conventional chemotherapy, or to proceed to bone marrow harvesting followed by ablative chemotherapy and ABMT.

CCG-3891 is significant for providing a reliable evaluation of the role of autologous BMT for neuroblastoma (and by extension, other pediatric solid tumors in which the primary tumor has metastasized). Non-randomized studies evaluating BMT for neuroblastoma have suggested that this expensive and toxic therapy may improve outcome. However, these studies are susceptible to patient selection biases, and the apparent observed benefit for BMT may be related to these biases rather than to the treatment itself. If improvements are to be made in the treatment of children with neuroblastoma, it is important to know whether further efforts should build upon an ABMT strategy or whether new strategies unrelated to ABMT need to be evaluated.

The CCG-3891 study began patient accrual in January, 1991 and should complete accrual in 1996, with almost 400 patients randomized between ABMT and conventional chemotherapy. CCG investigators deserve much credit for maintaining equipoise and for subjecting the ABMT strategy to a reliable evaluation via a randomized clinical trial.

INT-0154 - Evaluation of Intensified Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide in the Treatment of Newly-Diagnosed Ewing's Sarcoma or Primitive Neuroectodermal Tumor of Bone or Soft Tissue: does intensification of therapy improve outcome?

Significance - The primary objective is to evaluate in a randomized clinical trial the role of alkylator dose intensity in the treatment of Ewing's sarcoma, a very chemoresponsive tumor.

Retrospective evaluations for Ewing's sarcoma and for other pediatric solid tumors - e.g., osteosarcoma and neuroblastoma - have suggested that higher dose intensity is associated with improved outcome. However, the costs to the patient of increasing dose intensity are significant, both in the short-term - e.g., increased risk of severe infections - and in the long-term - e.g., increased risk of second malignancies. Thus, a reliable evaluation of the role of dose intensity for pediatric solid tumors is important, so that the potential benefits of dose-intensification can be carefully weighed against the increased toxicities associated with dose-intensive therapy.

The INT-0154 is an intergroup collaboration between the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG), and was opened to patient accrual in February, 1995. The study design calls for randomizing nearly 500 patients over a 4.7 year period.

POG 9404 - T-Cell #4 Protocol--Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced Stage T-Cell Non-Hodgkin's Lymphoma: does high dose methotrexate (HD-MTX) improve outcome; does Zinecard protect against cardiotoxicity due to anthracyclines?

Significance - The POG-9404 study for children with T-cell ALL uses a factorial design to evaluate two questions of therapy: (1) the role of HD-MTX when added to the an effective multi-agent chemotherapy backbone developed at the Dana-Farber Cancer Institute; and (2) the role of the cardioprotectant Zinecard in preventing cardiotoxicity in children receiving an anthracycline-based regimen. Secondary objectives include evaluating the prognostic significance of minimal residual disease as detected by using TAL-1 proto-oncogene probes, and evaluating the role of p53 and p16 tumor suppressor genes in the etiology and response to therapy of T-cell ALL.

The POG-9404 is particularly important, with ramifications beyond the treatment of children with T-cell ALL and lymphoblastic lymphoma. Doxorubicin and other anthracyclines are effective agents for childhood cancers, but their use is associated with irreversible cardiac damage. Currently, the only strategy for minimizing the risk of doxorubicin-associated cardiotoxicity is to limit the cumulative doxorubicin dose. Zinecard, a ferrous chelator, has been shown to protect against doxorubicin-induced cardiotoxicity in both animal model systems and in adult patients. However, randomized clinical trials evaluating Zinecard in adult patients have suggested that the agent may compromise the anti-tumor activity of doxorubicin. Thus, the Zinecard question of the POG-9404 study, will provide crucial data about whether Zinecard can be used to allow doxorubicin to be given more safely while not compromising its anti-leukemia activity. If the study shows that Zinecard is able to do this, then it will be a major advance for pediatric leukemia therapy.

The study opens for patient accrual in April, 1996, with nearly 500 patients being randomized over the succeeding 4 year period.

POG 9421 - Phase III Evaluation of Standard versus High Dose Ara-C Induction, Followed by the Randomized Use of Cyclosporine A as an MDR Reversal Agent, Compared to Allogeneic BMT, in Childhood AML: does use of high dose AraC, and of cyclosporine A, improve outcome?

Significance - The POG-9421 protocol uses a factorial design to address the following questions of therapy: (1) to determine the effect on 2-year continuous complete remission (CR) rate of 3 cycles of consolidation therapy, with and without the multi-drug resistance (MDR) modulator cyclosporine A (CSA); and (2) to determine the effect on CR rate and 2-year EFS rate of high dose versus standard dose Ara-C during induction. MDR expression studies will be performed on all patients at the Children's Hospital of Michigan.

The CSA question of therapy builds upon previous POG experience with the mitoxantrone/etoposide combination given with CSA (continuous infusion) in children with relapsed AML. The response rate was approximately 50%, irrespective of expression of the MDR by leukemic blast cells, suggesting that CSA was able to overcome the negative effect associated with expression of the MDR gene.

Although non-randomized studies have suggested benefit in some settings for use of an MDR-reversal agent, the POG study will be one of the first large randomized studies to reliably address this question and will be a definitive test for this treatment strategy in a disease setting for which compelling rationale exists for its evaluation. The correlative laboratory studies evaluating MDR expression will be a critical component of the study, and their successful accomplishment will greatly add to the importance and interpretability of outcome data from the study.

The POG-9421 study opened for accrual in February, 1995 and will enter patients for 4 years, for a total accrual of 560 patients.

POG 9457, INT 0145, CCG 7943 - Does the topoisomerase-I inhibitor topotecan merit investigation in Phase III trials of pediatric solid tumors?

Significance - A critical area of clinical research in pediatric oncology is the evaluation of the topoisomerase-I inhibitors for specific childhood tumors. This new class of agents has a mechanism of action that is distinctive from all other agents currently used as standard therapy for pediatric cancers. Pre-clinical studies have demonstrated that these agents are highly cytotoxic against solid tumors such as rhabdomyosarcoma and neuroblastoma. Early clinical trials with topotecan have confirmed significant activity towards advanced stage neuroblastoma, as demonstrated by a study conducted by the Pediatric Oncology Group in which tumor responses were seen in over 60% of patients with neuroblastoma. Furthermore, tumor responses to the combination of topotecan given with cyclophosphamide have been observed in patients with Wilms' tumor, rhabdomyosarcoma, neuroblastoma, and osteosarcoma. Phase II trials further clarifying the anti-tumor activity of topotecan for pediatric solid tumors are ongoing for osteosarcoma, neuroblastoma, Ewing's sarcoma, and rhabdomyosarcoma. Results from these phase II trials will provide critical data to be used in deciding whether larger randomized phase III trials of topotecan to reliably determine its contribution to curative therapy are warranted.

OVARIAN CANCER

GOG 152 - Does surgical cytoreduction following 3 cycles of chemotherapy improve outcome in patients with residual tumor?

Significance - It has been suggested that chemical cytoreduction with chemotherapy may facilitate surgical cytoreduction. A decrease in tumor burden at initial surgery has been shown to prolong survival in patients with advanced ovarian

cancer. Interval surgical cytoreduction for patients initially only partially debulked might improve outcome, and prior chemotherapy might increase resectability. The GOG has opened a phase III trial in which patients with suboptimally debulked stage III ovarian cancer are treated with 6 cycles of cisplatin/taxol, + secondary surgical cytoreduction after 3 cycles

INT-xxx - Does high-dose chemotherapy with stem cell support benefit patients with ovarian cancer?

Significance - Phase II studies suggest that "bone marrow transplant" regimens in ovarian cancer improves outcome for women with minimal residual, platinum-sensitive disease. GOG, ECOG, and SWOG are developing a phase III trial for women with platinum-sensitive, minimal residual disease after primary platinum/taxol therapy. They would be randomized to consolidation taxol or a high-dose regimen of mitoxantrone, cyclophosphamide and carboplatin. This should provide a reliable determination of the benefit, if any, of this strategy.

GOG 158 - Can a simpler taxol/platinum regimen be substituted for the current standard?

Significance - The optimum dose and schedule for paclitaxel (taxol) in the primary treatment of women with advanced ovarian cancer has not been established. The GOG has opened a phase III trial evaluating its new "standard", taxol infused over 24 hours with cisplatin vs a less toxic and less expensive regimen, 3 hour taxol and carboplatin, in patients with optimally debulked stage III ovarian cancer.

CERVICAL CANCER

GOG 141 - Does neoadjuvant chemotherapy improve outcome for cervical cancer patients?

Significance - Phase II studies have demonstrated high response rates to neoadjuvant chemotherapy. The impact of these chemotherapy regimens on survival is not clear. The GOG is currently conducting a phase III trial of radical hysterectomy with pelvic lymph adenectomy with or without neoadjuvant vincristine and cisplatin chemotherapy.

GOG 120 - Which radiosensitization regimen optimizes outcome?

Significance - Previous studies have suggested increased response to radiotherapy associated with radiosensitizing agents. The optimal regimen of agents has not yet been established. The GOG currently has a phase III trial of hydroxyurea vs hydroxyurea, 5FU infusion and bolus cisplatin vs weekly cisplatin as adjunct to radiation therapy in patients with advanced cervical cancer.

GOG 109, SWOG 8797 - Does adjuvant chemotherapy following hysterectomy improve outcome?

Significance - Chemotherapy has activity in patients with advanced recurrent cervical cancer. The role of chemotherapy as adjuvant treatment has not been established. The RTOG has a phase III trial in which patients at high-risk for para-aortic lymph node metastasis are randomized to pelvic radiation therapy with chemotherapy vs pelvic and para-aortic radiation. The SWOG and GOG have an intergroup study for patients with stages IA2-IIA cervical cancer who are randomized to radiotherapy + 5FU infusion and bolus cisplatin after radical hysterectomy.

ENDOMETRIAL CANCER

GOG 139 - Does circadian-timed chemotherapy improve response to chemotherapy?

Significance - Phase II trials have suggested decreased toxicity and improved response associated with circadian-timed chemotherapy. To date, there are no phase III data evaluating circadian-timed therapy. The GOG is therefore currently conducting a randomized study of doxorubicin plus cisplatin vs circadian-timed doxorubicin plus cisplatin in patients with primary stage III and IV and recurrent endometrial cancer.

GOG 122, GOG 156 - Which adjuvant modality is superior: radiation therapy vs systemic chemotherapy?

Significance - Endometrial cancer is sensitive to both radiotherapy and chemotherapy. Unclear, however, is which modality is more effective as adjuvant therapy following hysterectomy. The GOG is currently conducting two phase III trials which compare these two modalities. In the first, patients found to have advanced endometrial cancer at time of hysterectomy are randomized to whole abdominal radiotherapy vs combination doxorubicin-cisplatin chemotherapy. In the second trial, patients with Stage I and II disease at hysterectomy are randomized to adjuvant pelvic radiation vs doxorubicin plus cisplatin.

GOG 9206 - Is minimal access surgery safe and effective for the diagnosis, staging and treatment of endometrial cancer?

Significance - Laparoscopic surgery has become increasingly prominent in general surgery as well as in gynecology. The safety and efficacy of minimal access surgery in the diagnosis, staging, and treatment of cancer has not been established. The GOG won funding through an NCI-sponsored RFA to support a phase III trial in which women with endometrial cancer would be randomized to standard hysterectomy and lymph node sampling vs laparoscopic-assisted vaginal hysterectomy and lymph node sampling.

NON-SMALL CELL LUNG CANCER

INT 0125 - Will 13-Cis Retinoic Acid prevent second primary tumors in Stage I Non-Small Cell Lung Cancer?

Significance - Preclinical and exploratory trials suggested that retinoids might prevent the development of second primary tumors. The investigators are conducting a large (approximately 1200 patient) intergroup randomized trial to determine if the incidence of second primaries could be reduced with a retinoid.

INT 0115 - Will postoperative adjuvant therapy improve outcome for patients with completely resected Stage II and Stage IIIA non-small cell lung cancer?

Significance - There is a 40-60% recurrence rate in patients with stage II/IIIA non-small cell lung cancer treated with surgery alone. Does adjuvant chemoradiotherapy improve locoregional control, decrease distant metastases, and yield an improvement in overall survival?

INT 0139 - Concurrent Chemotherapy Plus Radiotherapy, vs Concurrent Chemotherapy Plus Radiotherapy Followed by Surgical Resection for Stage IIIA (N2) Non-Small Cell Lung Cancer: does surgery improve outcome?

Significance - Bulky, locally advanced non-small cell lung cancer is usually treated with non-surgical modalities, but there is a high recurrence rate, suggesting that deposits of micro-metastatic disease exist that are not affected by the current approaches to therapy. In addition, patients with mediastinal lymph node involvement found at the time of mediastinoscopy, and treated with surgery alone, have poor long-term prognosis. Several small randomized trials have suggested that neoadjuvant therapy might yield improved survival in patients with non-small cell lung cancer. The above trial is being performed in carefully staged patients, testing the regimen of concomitant chemoradiotherapy followed by surgery vs chemoradiotherapy (standard control), to determine if surgery leads to improved locoregional control and overall survival.

SMALL CELL LUNG CANCER

CALGB 9430, NCCTG-932051, NCCTG 932053, SWOG 9242, CALGB 9332, E7593 - What is the activity of the following agents?

CALGB 9430: Novel Doublets in Extensive Small Cell Lung Cancer: A Randomized Phase II Study of Topotecan/Cisplatin, Paclitaxel/Cisplatin, and Paclitaxel/Topotecan

NCCTG 932051: A Phase II Study of Taxol and Cisplatin in Previously Untreated Patients with Extensive-Stage Small Cell Lung Cancer

NCCTG 932053: A Randomized Phase II Trial of Different Schedules of Topotecan for the Treatment of Extensive-Stage Small Cell Lung Cancer

SWOG 9242: Evaluation of Taxotere in Small Cell Lung Carcinoma

CALGB 9332: A Phase II Trial of Navelbine or Navelbine Plus Doxorubicin in Previously Treated Patients with Small Cell Lung Cancer

E7593: Cisplatin Plus Etoposide vs Cisplatin Plus Etoposide Followed By Topotecan in Extensive-Stage Small Cell Lung Cancer: A Phase III Trial

Significance - The above 6 trials (5 are phase II, the latter is phase III) are testing new agents with novel mechanisms of action in extensive stage small cell lung cancer, with the goal of developing more effective therapy that will improve overall survival. The agents are being tested both singly and in combination with drugs that have shown synergy in preclinical systems.

NCCTG 892052 - Is accelerated hyperfractionated split course thoracic radiation therapy superior to standard fractionated thoracic radiation therapy when given in conjunction with chemotherapy in limited small cell carcinoma of the lung?

Significance - A prior intergroup trial in limited small cell lung cancer showed no short-term improvement in overall survival but an improvement in locoregional control in twice vs once daily radiotherapy given in conjunction with chemotherapy. Longer term follow-up from the closed trial is needed; this is a complementary study evaluating a modified fractionation schedule.

HEAD AND NECK CANCER

RTOG 9115 - Is low-dose 13-Cis Retinoic Acid effective in preventing second primary tumors?

Significance - The occurrence of second primaries is common in patients with resected, early stage head and neck cancer. Based on preclinical and small randomized trials, the investigators are conducting a large randomized trial (approximately 1200 patients) asking if treatment with a daily oral retinoid can prevent second primaries.

RTOG 9111 - Which of 3 strategies for larynx preservation may improve survival?

Significance - Based on the extent of organ preservation with preserved survival from the VA Cooperative Study Program's randomized trial of immediate surgery vs induction chemoradiotherapy with surgical salvage in patients with laryngeal cancer, the investigators are conducting an intergroup randomized trial comparing induction chemotherapy and radiation therapy vs concomitant chemotherapy and radiation therapy vs radiation therapy.

RTOG 9003 - Will an altered fractionation schedule of XRT improve survival in the unresectable patient?

Significance - This randomized study compares twice daily hyperfractionation, accelerated hyperfractionation with a split and accelerated fractionation with concomitant boost to standard fractionation radiotherapy for squamous cell cancer of the head and neck.

RTOG 9501 - Will addition of chemotherapy reduce locoregional recurrence in patients with resectable high risk squamous cell cancer of the head and neck?

Significance - A menu of past clinical trials have evaluated radiotherapy +/- chemotherapy in the resectable patient, and have shown a decrease in distant metastases but no impact on overall survival. Given the significant morbidity associated with local recurrences in the head and neck cancer patient, the investigators are conducting a randomized trial only in those patients at high risk for recurrence to ask whether chemotherapy can decrease the incidence of locoregional recurrence. Secondary endpoints will determine the incidence of distant metastases and overall survival.

RTOG 9407 - Will pentoxifylline decrease radiation related soft tissue necrosis?

Significance - A current modality with efficacy in the head and neck cancer patient is radiotherapy, but the modality is limited by side effects such as soft tissue necrosis. The IL-1 antagonist has preclinical evidence to suggest promising activity, and the investigators are conducting a randomized trial to determine if pentoxifylline can decrease the incidence of soft tissue necrosis related to radiotherapy.

BLADDER CANCER

INT 0080, RTOG 95-06 - Does neoadjuvant therapy improve survival for invasive bladder cancer, and can some patients be spared cystectomy?

Significance - Although advanced bladder cancer has been transiently responsive to combination chemotherapy, and although there are several newly identified active agents in transitional cell cancer, it remains to be determined whether we can substantially improve survival or morbidity from cystectomy, by applying these agents earlier when invasive disease is first diagnosed.

The question of the value of neoadjuvant therapy for bladder question is a very timely one this year during which the MRC/EORTC randomized trial and the INT phase III trial will be analyzed. The results of these studies will determine the direction of the next generation of trials, either toward building on a positive result or going back to the drawing boards until some of the newer agents have been

developed into promising new combinations. Meanwhile, RTOG's pilot phase I/II trial is attempting to replicate startlingly positive results in a French trial of neoadjuvant chemoradiation. If this confirms a high rate of bladder preservation without loss of tumor control it will clearly open a new direction for subsequent studies.

RENAL CELL CANCER

T93-0198 - Does 13-cis-retinoic acid improve response in patients with advanced renal cell cancer treated with IFN alpha 2A?

Significance - This confirmatory study is predicated on encouraging phase II results demonstrated by MSKCC for the combination regimen .

SWOG 8949 - Does prior nephrectomy improve outcome of patients with advanced renal cell cancer treated with Intron-A?

Significance - This randomized comparison of Intron-A preceded by nephrectomy, vs Intron-A alone will test if there is a rationale for aggressive surgery in patients with advanced renal cell cancer. Phase II studies have suggested that biologic therapies are more effective against metastases once the primary tumor has been removed in this disease. Traditionally, nephrectomy has not been found to offer effective palliation in asymptomatic patients with advanced disease.

ADULT LEUKEMIA

SWOG 9328 - What is the role of adoptive immunotherapy with interleukin-2 following high dose chemotherapy with autologous transplantation for patients with AML beyond first remission?

Significance - Although autologous transplantation may salvage a proportion of patients with relapsed AML, most eventually recur and die from their disease. Pilot trials with single agent IL-2 demonstrated activity in relapsed and refractory patients with AML. Studies conducted at the University of Washington suggest that patients with AML treated with IL-2 after salvage therapy may experience a second remission longer than the first, suggesting benefit from the lymphokine. Since it is believed that biological therapies will be most effective in the setting of minimal residual disease, this trial will examine the efficacy of IL-2 post-autologous transplantation.

This study would serve to confirm the efficacy of adoptive immunotherapy in patients with AML and would provide a foundation for new therapeutic strategies earlier in the course of the disease.

ADULT NON-HODGKINS LYMPHOMA

CALGB 9254 - What is the effect of an immunotoxin following high dose chemotherapy with autologous stem cell transplantation on relapse rate and survival in patients with B-cell NHL?

Significance - The majority of patients with NHL who are treated with an autologous transplant for salvage therapy still recur and die from their disease. Interesting studies were published from the Dana Farber Cancer Center using the ricin toxin conjugated to the anti-B-cell monoclonal antibody (immunoconjugate). This compound, B4-blocked ricin [B4BR], appeared to suppress the expression of the bcl-2 gene expression following transplant in patients with minimal residual disease. Overexpression of this gene is characteristic of patients with follicular lymphomas and CLL, and its protein inhibits apoptosis. This study will compare the use of B4BR versus no additional therapy after autologous transplantation

This study will, first, attempt to confirm the promising pilot data, second, it will better characterize the implications of minimal residual disease following transplantation, and, thirdly, it will assess the role of immunoconjugate therapy in these patients. This study is the first of a series of trials which would use more effective agents as they become available.

SWOG 8809 - Will an intensive combination of chemotherapy, radiotherapy, and biological therapy prolong the survival of patients with advanced stage, indolent NHL?

Significance - Patients with indolent NHL are incurable with conventional therapies, or even autologous bone marrow transplantation. One attractive strategy is to attempt to reduce the patient to a state of minimal residual disease with intensive chemotherapy, consolidate the response with radiation therapy, and to eradicate minimal residual disease with a biological response modifier with known efficacy, alpha-interferon

This study will provide the first evidence as to whether aggressive treatment is the answer to the incurability of indolent NHL.

SWOG 9438 - What is the benefit of adoptive immunotherapy with IL-2 following autologous transplantation in patients with non-Hodgkin's lymphoma?

Significance - Patients with NHL who fail to enter a remission or who relapse after having achieved a remission are infrequently salvaged with standard dose regimens. The efficacy of autologous transplantation appears limited to those patients who retain chemosensitivity following recurrence; nevertheless, only a

fraction of that cohort are cured with autologous transplantation. The lymphokine IL-2 has demonstrated single agent activity against NHL. This study will address the potential for IL-2 to eradicate minimal residual disease following autologous transplantation and, therefore, potentially prolong the survival of these patients.

This trial will determine if the curative potential of autologous transplantation can be augmented by adoptive immunotherapy. If a beneficial effect is identified, this strategy will be evaluated earlier in the course of the disease.

MULTIPLE MYELOMA

INT 0141 - Is high dose chemotherapy with stem cell support superior to standard chemotherapy as the initial treatment of patients with multiple myeloma?

Significance - Multiple myeloma is a uniformly fatal disease with a median life expectancy of 3 ½-4 years. No recent therapies have improved on this outcome. Recent phase II studies in the U.S. and abroad have suggested that high dose chemotherapy with autologous stem cell support or allogeneic transplants in select patients may prolong survival. This protocol randomizes patients to either autologous stem cell transplantation or standard therapy, while appropriate candidates with an HLA match receive an allogeneic transplant.

If the results of the phase II trials can be confirmed, the use of high dose therapy provides the first therapeutic improvement in myeloma in recent years. In addition, it would provide the foundation for new strategies employing high dose therapy and gene therapy. If the trial is negative, it would limit the number of these transplants performed outside of a clinical research setting.

E1A95 - What is the role of the multi-drug resistance reversing agent PSC-833 in the treatment of patients with relapsed or refractory multiple myeloma?

Significance - Plasma cells from the majority of patients with multiple myeloma who have failed front-line therapy express the *mdr* phenotype. Previous attempts at reversing this resistance *in vivo* have been unsuccessful, primarily because of drug toxicities. PSC-833 lacks the immunosuppression, myelosuppression, cardiac and liver toxicity encountered with the previously used agents.

If this study demonstrates reversal of drug resistance with a clinically tolerable agent, studies would be developed to prevent the emergence of drug resistance by administration of the agent during initial treatment for the disease.

MELANOMA

SWOG 9035 - Will immunotherapy with allogeneic melanoma vaccine for patients with intermediate thickness, node negative melanoma (T3N0M0) improve outcome?

Significance - Patients with this stage melanoma experience approximately 25% recurrence rate at 5 years if treated with surgery alone. This trial uses a novel vaccine preparation (Melacine) following surgery in intermediate risk patients, and is randomized against surgery followed by observation.

EST 1690 - Does post-operative adjuvant interferon alpha 2 improve outcome in resected high-risk primary and regionally metastatic melanoma? Which of 2 doses of interferon gives superior results?

Significance - Patients in this risk group experience approximately 45-50% recurrence rate at 5 years. This study randomized patients to high dose IFN vs. chronic low dose IFN (3MU/d 3 x/wk sc for 2 yrs) vs observation. This study seeks to corroborate the positive findings from EST-1684 and has several companion studies which are aimed to address the mechanism of IFN action, the prognostic implications of tumor ploidy and proliferative activity, and study of the host mononuclear cell activation.

T96 0010 - Does the combination of cisplatin, dacarbazine, carmustine and tamoxifen improve results over those obtained with dacarbazine alone in patients with advanced melanoma?

Significance - The four drug regimen (commonly referred to as the Dartmouth regimen where it was initially developed) has shown promising results in several small phase II trials. However, these results have not been duplicated in phase II Cooperative Group trials. This trial should definitively test the Dartmouth regimen, which has become widely used in the oncologic community, against the accepted standard of dacarbazine (DTIC).

CR96-003 - Does concurrent biotherapy with DTIC, DCCP, VBL, IL-2 and IFN improve outcome compared to chemotherapy alone in metastatic melanoma?

Significance - This new study is still under review but the basic concept is to perform a definitive test of combination biologic therapy and chemotherapy compared to chemotherapy alone. Several phase II studies have suggested that combination therapy results in higher complete response rates and more long-term, durable remissions. However, these trials are small and selection bias may account for the improvement that has been noted.

E 1694 - Is adjuvant ganglioside vaccination therapy superior to IFN alpha 2b for treatment of high-risk melanoma?

Significance - This study will evaluate whether vaccination against melanoma gangliosides, a fairly non-toxic therapy, is superior to therapy with the high-dose IFN regimen. Levels of IgG and IgM antibodies to the vaccine will be studied as intermediate endpoints. A small, randomized trial done at Memorial Sloan Kettering did demonstrate that this vaccine was effective in reducing

recurrences from melanoma.

CENTRAL NERVOUS SYSTEM TUMORS

NCCTG 86-72-51, NCCTG 94-72-53 - What is the relative efficacy and toxicity of high dose versus low dose cranial radiation for low-grade gliomas (astrocytomas, oligodendrogliomas, and mixed tumors); b) what is the role of diagnostic and prognostic markers in low-grade gliomas?

Significance - Management of these lesions remains extremely controversial. Median survivals are in the range of 5-7 years and the majority of tumors ultimately recur and/or become more aggressive. The role of radiotherapy is debated both because the benefit is uncertain and because cognitive dysfunction after radiation is a major problem in patients who survive for a period of years. An Intergroup trial in the 1980s (BTCG 8730) attempted to randomize between early and delayed RT but was unable to accrue patients because of clinician biases (in both directions).

NCCTG 86-72-51 randomized patients (other than those with pilocytic tumors) between 6480 cGy and lower dose RT of 5040 cGy. The companion protocol (NCCTG 94-72-53) is evaluating histologic and molecular markers in relation to prognosis. It is hoped that the outcomes of these trials will allow future studies to address prospectively whether radiation can be delayed in specific subgroups, and whether there are subgroups appropriate for randomized evaluation of chemotherapy.

RTOG 93-05 - Is there benefit from adding stereotactic radiosurgery (SRS) boost to conventional external radiation and BCNU chemotherapy in therapy of newly diagnosed glioblastomas?

Significance - SRS has demonstrated efficacy for vascular lesions and for small numbers of cerebral metastases but has also been widely and uncritically adopted into clinical management of gliomas.

The very high and very focal RT dose that can be achieved can certainly control tumor locally, but this phase III trial should be able to establish whether or not this leads to genuine benefit in high grade gliomas, which are highly resistant to current therapy and typically infiltrative.

INT-xxx - Will the use of stereotactic radiosurgery (SRS) lead to some durable survivorship in patients with limited cerebral metastases and no progressive disease outside the CNS?

Significance - The demonstration in randomized trials that a proportion of patients with surgically resectable cerebral metastasis can achieve durable survival with surgery and RT has fostered the hope that something similar can be achieved for unapproachable lesions, or 2-3 lesions, by utilizing SRS as a substitute for

surgical resection. Other studies recently completed will also help formulate the future management of this very common clinical problem: INT-0124 investigated whether RT can be omitted when surgery has been performed; RTOG-91-04 examined accelerated hyperfractionated RT compared to conventional fractionation.

SWOG and RTOG are planning to study this question in randomized trials, which may be combined into a single Intergroup trial.

NCCTG 90-72-52, 94-72-52 and SWOG 9218 - What are the potential roles for diagnostic and prognostic markers in high-grade gliomas treated with conventional radiation and nitrosourea therapy?

Significance - Anaplastic Astrocytomas and Anaplastic Oligodendrogliomas, as well as mixed anaplastic tumors, are now identified as having probably both better natural history and greater response to current therapies than glioblastomas. However, histopathologic uncertainty and tumor heterogeneity make reliable classification by light microscopy difficult at best. Recent evidence suggests that molecular markers have the potential to more definitively classify these tumors - e.g. 9p deletions appear to correlate with oligodendrocytic behavior and response to therapy, while 9q deletions appear to be indicative of astrocytic lineage. Measurement of tumor alkyltransferase (O^6 -MGMT) activity appears able to identify a subset of patients more likely to respond to nitrosourea therapy and, moreover, should allow rationale testing of new therapeutic agents that can overcome tumor resistance by inhibiting alkyltransferase-mediated repair of DNA damage.

These studies, therefore, should be of importance in subclassifying glioblastoma, clarifying their complex biologic behavior, selecting appropriate patients for clinical trials, and eventually for selecting specific therapeutic approaches.

INT-0149 - Does adjuvant chemotherapy prolong survival for anaplastic oligodendrogliomas?

Significance - This is the first large scale trial ever performed in this somewhat rare brain tumor but is of importance because of the unusual responsiveness to therapy that makes it feasible to consider that overall survival rates can be substantially improved by the addition of PCV chemotherapy.

Eventually it may be possible to attempt to study whether we could maintain good survival results while minimizing cognitive dysfunction by delaying brain radiation. The current trial also serves as a model of both Intergroup and international collaboration to study a disease for which phase III trials would otherwise not be possible.

AIDS MALIGNANCIES

GOG 155 - What is the efficacy of Alpha-Interferon and Isotretinoin with or without Zidovudine (AZT) in the treatment of HIV-infected women with invasive cervical carcinoma?

Significance - Based on promising results with these agents in the immunocompetent population, the investigators are studying whether these same, non-myelosuppressive therapies may result in significant response and survival in patients infected with HIV (Phase II trial).

POG 9362 - What is the efficacy of Alpha-Interferon in HIV-related malignancies in children?

Significance - Based on promising results in the organ transplant setting with lymphoproliferative disease, the investigators are evaluating the role of a biologic in children with lymphoproliferative disease infected with HIV.

E2D94 - What is the efficacy of 9-aminocamptothecin in patients with AIDS-related Kaposi's sarcoma?

Significance - Topoisomerase I inhibitors may have both anti-HIV and anti-tumor effects. The investigators are testing this new agent with a novel mechanism of action in a commonly occurring AIDS malignancy.

E1493 - Does chemotherapy added to standard radiotherapy improve response in patients with primary CNS lymphoma?

Significance - Radiotherapy is the standard unsatisfactory approach in this clinical setting. In the immunocompetent patient neoadjuvant chemotherapy improves survival. Feasibility and outcome are now being evaluated in Immunocompromised patients.

CLINICAL TRIALS FUNDING

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Klausner: The estimated clinical trials budget for FY97 is \$391,685,000 including both treatment and prevention clinical trials. This amount is 16% higher than the FY94 actual amount of \$339,003,000. The FY95 actual of \$384,817,000 is 2% lower than the FY97 estimate. The FY96 estimate of \$390,811,000 is approximately level with the FY97 estimate.

MINORITIES IN CLINICAL TRIALS

Mr. Stokes: What is the institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Klausner: The NCI is committed to guaranteeing the enrollment of minorities and women in clinical trials. As evidence of the Institute's commitment, we have completed an analysis of incidence and mortality of cancers that examine 12 different ethnic and racial groups. This information will serve as a guide for the proper research questions that need to be addressed.

The NCI has analyzed participation in treatment trials. The analysis illustrates that the proportion of minorities participating in NCI treatment trials around the United States is proportional to the incidence of disease in those population. As part of NCI's treatment trials, the Cooperative Group studies is closely monitored to ensure that accrual includes appropriate numbers of minority and female patients. Two of the nine NCI-sponsored clinical trials cooperative groups, the National Surgical Adjuvant Breast and Bowel Project and the Gynecologic Oncology Group, focus on cancers occurring exclusively in women. The Minority Initiative Program helps the Clinical Trials Cooperative Groups reach out to minority populations through community outreach, translators, staff training, and preparation of culturally sensitive materials.

NCI's Cancer Prevention Program funds two programs, the CCOPs and the Minority-Based CCOPs to help extend access of clinical trials from teaching hospitals into community practices. These activities are coordinated with the efforts of the NCI's Office of Cancer Communications. In addition, the Office of Cancer Communication continues to collaborate with 166 community organizations around the country to provide cancer diagnosis and treatment information targeted at minority and underserved populations. Additional efforts are underway to increase the number of minority individuals who are enrolled on cancer prevention trials.

Within research conducted through the NCI's intramural program, specific progress and efforts have been instituted toward minorities and women in clinical trials. The NCI's Pediatric Branch has initiated the Minority Adolescent HIV Research Project as a major component of the Institute's effort to establish a comprehensive clinical research program for HIV-infected adolescents. In addition to creating a national model for the treatment of the adolescent mother-child dyad, this program will increase knowledge about the clinical manifestations and natural history of adolescent HIV infection.

Seroepidemiologic studies suggest that heterosexual transmission is the next wave of the HIV epidemic, one in which adolescents, minorities and young adult women are increasingly and disproportionately represented. Recent epidemiological studies of adolescent HIV rates in the District of Columbia performed by Dr. Larry D'Angelo of Children's National Medical Center reveal that in 1994-1995 approximately 4.76% of males and 4.60% of females were seropositive for HIV

infection. Clinical research trials are needed to investigate the pathophysiology of HIV infection and determine appropriate treatment interventions in the adolescent population. Unfortunately, very few HIV-infected adolescents have been enrolled in research protocols, in part due to lack of protocols and programmatic efforts designed specifically for adolescents.

The Minority Adolescent HIV Research Project provides access to populations historically under represented in NIH clinical research trials: Minority adolescents of African American and Hispanic descent; adolescent females of all racial groups; adolescents from the District of Columbia, Baltimore and surrounding local communities; pregnant HIV-infected adolescents and their infected offspring of all racial groups. It also provides access to clinical research for the medically under-served HIV-infected adolescent and infant population of the District of Columbia, the majority of whom belong to ethnic or racial minority groups. The participation of minorities, adolescents and females, who are disproportionately affected by HIV disease, in research will provide data concerning drug pharmacokinetics, pharmacodynamics and disease pathophysiology which may highlight differences that may exist due to genetic constitution, gender or hormonal influence.

The Minority Adolescent HIV Research Project is being implemented through a contract mechanism with the Hospital for Sick Children, Washington, D.C. A comprehensive multidisciplinary clinic opened in June 1995. In addition to education and outreach activities, HIV testing and counseling as well as access to comprehensive obstetric and gynecologic services are provided. Since its opening, over 263 teens have received comprehensive medical care and services through the clinic. A "menu" of HIV clinical trials has been established through collaboration with Children's National Medical Center and Washington Hospital Center providing access to additional pediatric trials, adolescent specific trials and transmission trials for HIV-infected pregnant adolescents. Two investigative treatment protocols addressing the scientific agenda outlined above received final NCI Investigational Research Branch's approval in September 1995 and are open for enrollment.

Approximately 70 teens have undergone HIV testing and counseling since the clinic opened and four HIV positive teens have been identified. They are currently being evaluated for protocol eligibility and enrollment.

The NCI is in the process of establishing a collaboration with Howard University, based on the study of metastatic prostate cancer in minority populations. The purpose of this collaboration is to introduce into the minority patient population the opportunity to participate in state-of-the-art clinical drug therapy trials, and concurrently address molecular issues that relate to clinical response to therapy. The design of the collaboration is to co-write clinical therapy trials with Howard University personnel in the Departments of Pharmacology and Urology. Such trials

will include the following components: a) treatment of affected patients at the minority institution; b) procurement of prostate cancer tissues from such patients for molecular studies; c) training of Howard University personnel in the execution of such molecular studies; and d) collection of data to assess if there is a molecular origin for the long-noted ethnic differences in survival rates in this disease.

The molecular studies will include studies of the androgen receptor, studies of the androgen receptor mutation associated with resistance to hormonal therapy, expression of specific genes related to angiogenesis, and studies of specific genes related to metastatic potential and tumor cell aggressiveness.

The infrastructure is being put into place at this time to conduct this collaboration over a 2-5 year period, which will provide enough time for adequate patient accrual to address these types of questions.

MINORITY HEALTH PROGRESS

Mr. Stokes: For the disease and disorders that are under the purview of your institute, where do we stand today with respect to closing the gap in minority health, specifically what progress do you have to report to the subcommittee this year? Also, provide a more detailed response for the record, be as specific as possible?

Dr. Klausner: The NCI has done a great deal this year to address the critical issue of cancer rates among minorities. Past patterns of cancer incidence and mortality predict that a disproportionate share of U.S. incidence and mortality will be borne by minorities. Significant differences exist in cancer rates for many types of cancer among various U.S. populations. NCI's Surveillance, Epidemiology, and End Results--SEER--Program covers about 14 percent of the overall population, but by design includes substantially larger percentages of minority populations. The NCI recently released what we think is a landmark document, *Racial/Ethnic Patterns of Cancer in the United States, 1988-1992--SEER Monograph*, NIH Publication 96-4104--which reports cancer rates for Alaskan Natives, American Indians--New Mexico--, African Americans, Chinese, Filipinos, Japanese, Hawaiians, Koreans, Vietnamese, Hispanic, and white populations. We have looked at these different ethnic and racial groups and completely analyzed the incidence and mortality of cancers. The data provides a basis for monitoring cancer rates in diverse populations with unique cultures and lifestyles as well as possible unique genetic factors that may influence cancer risk, and will guide researchers in the development of appropriate research questions. Research studies will examine whether differences in cancer incidence may be due to such factors as different occupational or environmental exposures, or diet.

The SEER report found that the racial/ethnic groups were broadly similar on some measures of cancer. Overall, black men have the highest overall cancer incidence & mortality rates, largely due to the excess of prostate and lung cancer. Among women, cancer is most common among non-Hispanic whites, while the cancer death rate is highest in Alaskan Natives.

The report cites the five most frequently diagnosed cancers and the five most common causes of cancer death for each racial/ethnic group. Breast cancer ranks first in all groups of women except Vietnamese, who have a higher rate of cervical cancer. However, breast cancer incidence rates vary fourfold, from 28.5 per 100,000 Korean women to 115.7 per 100,000 non-Hispanic white women. In terms of mortality, lung cancer ranks first in most groups of women, and it is either in first or second place in all groups except American Indians. Breast cancer mortality ranks in the top two sites for all groups except Alaskan Native women, in whom it ranks third. Hispanic, Chinese, Filipino, and Japanese women have annual breast cancer mortality rates at or below 15 per 100,000, while black, white and Native Hawaiian women have rates above 25 per 100,000. Although mortality rates have declined at a greater pace among white than black women, it is encouraging that the most recent data indicate a decline in mortality among younger black women. Racial differences depend on several factors, including risk of developing breast cancer, access to screening and early detection, treatment and medical follow-up, and supportive care. To understand the respective roles of each of these factors, a number of investigations are currently underway to assess differential risk factors, patterns of care, and clinical and biologic prognostic factors for survival.

Among men, either prostate or lung cancer ranks first in each racial/ethnic group for both incidence and mortality. Prostate cancer incidence varies more than sevenfold, from 24.2 per 100,000 Koreans to 180.6 per 100,000 African-Americans. The high rate of prostate cancer in African-American men was emphasized in the RFA "Molecular Epidemiology of Prostate Carcinogenesis." This RFA resulted in several grants being funded through 1999. A major emphasis of these research efforts is the use of biologic markers to investigate risk factors that may differ among racial populations. Colorectal cancer incidence rates also vary substantially. The Alaskan Native rates are more than four times as high as the American Indian rates for both men and women. A few rare cancers appear in the top five sites for specific groups. Cancer of the gallbladder ranks fourth in American Indian women in New Mexico, while thyroid cancer is fourth among Filipino women. Nasopharyngeal cancer, which is common in China and Southeast Asia, occurs more frequently in Chinese and Vietnamese American men than in other groups.

The NCI is committed to reducing the cancer mortality disparity between disadvantaged populations. One approach to achieving this objective is through support to institutions for increasing their efforts to broaden minority participation in research activities and involvement in programs developing the latest and most effective measures in cancer prevention, cancer control, and clinical treatment

research. A primary goal is to support research as well as ensure that underserved and minority populations have access to the delivery of state-of-the-art cancer prevention and control information and treatment modalities. The programs and Request for Applications--RFAs--initiatives supported by the NCI are intended to ensure participation of minorities, by individuals representing all subpopulations in our society in all aspects of basic and clinical research as well as clinical trials programs. I'm pleased to report that a recent analysis of NCI treatment clinical trials around the country indicates that minorities are participating in those trials in proportion to the incidence of disease in the minority population.

Cancer prevention and control programs are underway which seek not only to lower the overall cancer rates, but target areas with high percentages of minority populations. These include the American Stop Smoking Intervention Study--ASSIST, 5 A Day for Better Health, and the Cancer Information Service, as well as the Community Clinical Oncology Program--CCOP-- and the Minority- Based CCOP. The NCI's Leadership Initiatives on Cancer are working with these programs to target Blacks, Hispanics and the low-socioeconomic regions of Appalachia.

Contributing to the cancer burden of U.S. minorities is their limited access for treatment to minority physicians with appropriate cultural sensitivities. This is largely due to the small numbers of U.S. minority clinical oncologists. Data from the American Medical Association for 1994 show that of 11,224 U.S. oncologists, only 184--1.6 percent--were of African American descent, 336--3.0 percent--were of Hispanic descent, and three--0.03 percent--were of Native American descent. Current statistics on medical specialties among U.S. medical school graduates do not portend a significant change in this situation. In 1994, only 11.2 percent of all medical school applicants were under represented minorities, a proportion that had not changed significantly from 10.8 percent in 1988. It is therefore imperative that a sufficient number of minority oncologists be available so that access to care is not limited by a lack of sensitivity to cultural issues. NCI's Comprehensive Minority Biomedical Program initiates grant programs which are intended to bring more women and minority participants into cancer research, and this year published several RFAs to promote minority participation.

CLINICAL TRIALS FOR AT RISK POPULATIONS

Mr. Stokes: Are there specific trials underway to address cancer in at risk populations?

Dr. Klausner: NCI has a study designed to identify people at high risk for lung cancer using hormonal markers that have been shown to become elevated with lung cancer, and by using novel bronchoscopic techniques that may have far more sensitivity than conventional methods for early identification of lung cancers. In addition, we have collaborative studies with the National Center for Human Genome Research to look at patients with strong family histories for colorectal cancer and the possibility of mutations in mismatch repair genes.

Within the NCI research program, the following trials are underway or have been recently completed to assess specific cancer types in at risk populations:

Breast Cancer Prevention Trial: The BCPT is a randomized clinical trial that is testing the effectiveness of tamoxifen for preventing breast cancer. Since June 1992, twelve thousand women at increased risk of developing breast cancer, based on factors such as age, family history, and personal history, have entered the study. Twenty percent of BCPT participants have two or more first-degree relatives - mothers, sisters, daughters - with a history of breast cancer, thus providing a unique resource for understanding breast cancer genetics. The average relative risk for BCPT participants is about five times as great as that for a comparable group of individuals in the general population. If proven effective, tamoxifen could provide an option to prevent breast cancer in certain women at high risk of developing the disease. Each woman participating in the BCPT is scheduled to take tamoxifen or placebo for five years.

Linxian Intervention Trial: NCI carried out a nutritional intervention trial to evaluate micronutrient supplementation on esophageal and gastric cancer in Linxian, China, where the rates of these malignancies are among the highest in the world. Results of this six-year study suggest that dietary supplementation with a combination of beta-carotene, vitamin E, and selenium was associated with a 21 percent reduction in mortality from gastric cancer. Further studies are planned to determine whether the positive effects persist after supplementation ends and whether particular subgroups benefitted more than others. In another intervention trial in Linxian, subjects with esophageal dysplasia who received multivitamin supplements were found to have increased reversion to normal cytology compared to controls.

Shandong Intervention Trial: NCI is conducting an ongoing intervention trial in Shandong Province, China, where the population is at high risk of stomach cancer. The trial is assessing the effectiveness of the following agents, alone or in combination, in inhibiting or reversing the progression of precancerous gastric lesions: amoxicillin/omeprazole therapy for *Helicobacter pylori* infection; dietary supplementation with vitamins C and E and selenium; and a garlic preparation.

Prostate, Lung, Colon and Ovary (PLCO) Cancer Screening Trial: The multisite screening trial will screen 37,000 men for prostate, lung, and colorectal cancers and 37,000 women for lung, colorectal, and ovarian cancers over four years. Genetic marker studies will be conducted on diagnostic biopsy specimens relating genetic aberrations of these cancers. The PLCO trial began accrual in 1993 and is planned to continue for 16 years. This time span includes 10 years of follow-up to determine the effects of screening on mortality for those four cancer sites.

Cervical Cancer Clinical Trial: In a randomized clinical trial of cervical cancer, an etiologic component to evaluate epidemiologic and laboratory indicators of progression from low-grade to high-grade cervical intraepithelial neoplasia (CIN) has been developed. The results should clarify the carcinogenic mechanisms involved in CIN, as well as enhance the development of cost-effective preventive measures.

Mother-to-Infant HIV Transmission Intervention Trial: A study of twin births revealed an elevated risk of HIV infection in the first-born twin, suggesting that the second born has less viral exposure as it passes through the birth canal. In a follow-up study in Malawi in collaboration with Johns Hopkins University, NCI investigators found that cleansing the birth canal with chlorhexidine did not reduce the overall transmission of HIV, but significantly reduced it in a subgroup of deliveries with prolonged rupture of membranes, suggesting a simple cost-effective approach to reducing pediatric HIV infection and AIDS.

Through NCI support, the following trials in at risk populations are proceeding:

Studies of Gastric Carcinoma: Dr. Pelayo Correa at Louisiana State University Medical Center is examining the role of antioxidants and *H. pylori* therapy in preventing progression of precancerous gastric lesions in a high-risk Colombian population living in the Andes mountains.

Diet and Genetic Alterations in Colorectal Neoplasia: Dr. Stanley Hamilton at Johns Hopkins University is evaluating the effects of high-fiber supplementation on genetic alterations in recurrent colon adenomas in high-risk subjects.

NCI MANAGEMENT CHANGES

Mr. Hoyer: I was very impressed to hear of the management changes you have made in the NCI. All of us here are concerned about improving the grant pay line, which you have done very effectively. How difficult were the changes to implement?

Dr. Klausner: The NCI underwent the single largest reorganization within the DHHS with relative ease. The Office of the Secretary, DHHS was outstanding in its support and assistance to NCI in handling this complex transformation. Through their assistance and the efforts of staff at NIH and NCI, the reorganization was completed and staff reassigned by October 1, 1995.

Complementing NCI's reorganization was the delegation of many administrative and management authorities that allowed the establishment of a flatter, more responsive organization. Again, the delegation of these authorities, forthcoming from all components of the DHHS and the NIH, allowed NCI to maximize streamlining opportunities that became available via the new organizational structure.

BARRIERS TO MANAGEMENT CHANGES

Mr. Hoyer: What barriers to change did you have to overcome?

Dr. Klausner: The most difficult barrier to overcome was the less tangible element of the "change in culture" resulting from the massive reorganization as well as the establishment of new scientifically based policies and procedures. NCI staff were impacted by tremendous changes in organizational structure, supervisory reporting and routine operations in a relatively short period of time (six months). Coping with these multiple changes for many of the staff has been a challenge but they have responded with enthusiasm, dedication, and good humor. They have embraced the changes with a positive attitude and optimism for the future. In an effort to involve the staff, NCI: a) established internal advisory boards to gain ongoing input from affected staff; b) established employee based working groups to address special areas of concern that have been raised; c) created newsletters to communicate information and; d) developed career development programs to enhance their future at the NCI. We have found that by involving employees in the process they have bought-in to the new ideas, supported innovation and have recognize the opportunities that can arise through the changes taking place throughout NCI.

STAFF RESPONSE TO MANAGEMENT CHANGES

Mr. Hoyer: Were the changes generally welcomed or resisted by staff?

Dr. Klausner: Any change of the magnitude that was undertaken naturally creates some apprehension. However, I am pleased to say that the overwhelming majority of staff recognized the need for change and were most supportive of our efforts. This was the most significant organizational change for the NCI since the passage of the National Cancer Act of 1971. The tremendous advancement of science in the intervening 25 years made this major realignment of the Institute's organization necessary to enable it to manage effectively the current scientific opportunities we now have before us. The staff, much to their credit, responded in an outstanding fashion to the needed adjustments.

EFFECTS OF MANAGEMENT CHANGE

Mr. Hoyer: How have the changes improved the management of the Institute and the science that is conducted, both through the intramural and extramural program?

Dr. Klausner: One of the main focuses of the reorganization was to simplify both structure and function in a way to facilitate science. The previous organizational structure resulted in barriers between Divisions due to the development of infrastructures that were required to manage each independent scientific program. The new structure has eliminated these barriers and established uniform procedures, processes and administrative support mechanisms that facilitate cooperation, collaboration and exchange of important information between all Divisions (both intramural and extramural). The improved communication and streamlined functions have already improved communication and interaction among scientific staff. Within the new structure, NCI has also collapsed the previous five Boards of Scientific Counselors (BSC) into two; a BSC that oversees intramural scientific operations and a Board of Scientific Advisors (BSA) that provides advice and guidance in executing extramural program activities. The Chairs of these Boards spend a significant amount of time at NCI, interacting with the Division Directors, program staff and each other on carrying out their responsibilities related to Board functions, including the execution of the scientific review process. The Chairs sit on NCI's Executive Committee, an important group that is extremely active in improving the management of NCI's scientific programs as well as improving interaction between NCI and its extramural constituency. This weekly interaction and discussion of NCI-wide issues has provided a powerful intellectual forum that is focused on improving the management of the Institute by identifying exciting scientific opportunities and providing critical evaluation and input into the daily operation as well as the strategic planning of the Institute.

NCI has also established two internal groups to facilitate improvements in science and administration. The Intramural Advisory Board and the Extramural

Advisory Board, essential elements of change and continuous improvement, are made up of NCI scientific staff who play an active role in identifying concerns and/or barriers to the efficient conduct of research and are chartered to help the Institute in developing recommendations that solve the problems in a way acceptable to the scientific community.

Finally, the Institute created the Office of Intramural Management and the Office of Extramural Management to provide a focused and improved approach to the administrative management and business support aspects of these two very different operations. Through the establishment of these offices, NCI has been able to eliminate six separate administrative management branches. The fragmented, feudal structure has been replaced with novel, full service Administrative Resource Centers which maximize the authorities delegated to Institutes thus streamlining and expediting the provision of support of both intramural and extramural scientific and program staff. This change has already resulted in reduced paperwork and time required for processing routine actions allowing the scientific staff more time to devote to their research endeavors.

SAVINGS FROM MANAGEMENT CHANGES

• Mr. Hoyer: How much money have you saved?

Dr. Klausner: One of our major concerns this year has been the need to increase the number of competing research grants that the Institute will fund. This need, coupled with a hard critical look at the activities supported through the contract mechanism and the in-house program, allowed us to identify approximately \$25 million which could be used to fund more competing Research Project Grants. As a result of these efforts, we are able to fund approximately 95 more grant applications than we originally estimated for this fiscal year. In so doing, we are able to fund additional research in a variety of research areas, including breast, prostate, and ovarian. Reorganization efforts also allowed the redistribution of contract and in-house funds to Cancer Centers and Clinical Cooperative Groups, to expand our efforts in AIDS malignancies, Genetics, and Informatics. As we continue to examine all of our work processes, and critically look at each of our programs, our hope is to be able to continue to redirect funds into the most promising areas of science to accelerate and build upon our knowledge base as rapidly as possible.

IMPACT OF MANAGEMENT CHANGES ON PAYLINE

Mr. Hoyer: What has been the impact on the payline?

Dr. Klausner: As a result of the past year's reorganization efforts, we have achieved cost savings in contracts, intramural, research management and support, and cancer control. With these savings and redirection, NCI anticipates a substantial increase in the payline for Research Project Grants--RPGs. The R01 payline is expected to go from 15.0 in 1995, to 23.0 in 1996. The RO1 is the core

investigator initiated vehicle that supports individual scientists across the country. In addition, it is expected that the success rate for all competing RPGs will be approximately 29% in 1996, as compared to the 21% success rate in Fiscal Year 1995.

AREAS FUNDED THROUGH SAVINGS

Mr. Hoyer: To what high-priority research areas are these funds dedicated?

Dr. Klausner: The National Cancer Institute is committed to peer-evaluated, investigator-initiated cancer research, and the increased paylines and success rates reaffirm that commitment. NCI researchers continue to explore the role of genetics, lifestyle, diet, and occupational and environmental exposures as they relate to cancer, while basic research increases our understanding of the biology of cancer. Breast, prostate, ovarian, cervical, lung, melanoma, and colo-rectal cancer research remain a high priority of the NCI's research program, in addition to childhood cancers.

INCREASED FUNDING THROUGH EFFICIENCY AND REDIRECTION

Mr. Hoyer: Can you provide the Committee with an estimate of the number of grants you have been able to fund that would not have been possible without these savings?

Dr. Klausner: The original payline for R01 Traditional Research Project Grants was established at the 18th percentile in December of this year. Increasing that payline to the 23rd percentile as a result of reorganization and cost savings will allow the funding of approximately 95 additional competing grants. In addition, the NCI has been able to redirect funds from contracts and in-house activities in order to expand research efforts in AIDS malignancies, cancer genetics, and informatics at the Cancer Centers and Clinical Cooperative Groups. Other re-directed funds will support expansion of the Community Clinical Oncology Program (CCOP), in addition to cancer research training and education.

EFFECTS OF INCREASING PAYLINE

Mr. Hoyer: Do you anticipate that making awards to a higher percentage of applicants will have an impact on the number and quality of grant proposals you receive?

Dr. Klausner: It is not possible to say what effect increasing the success rate by making more awards will have on the future number of applications. With the relatively low success rates in the recent past, many people have been discouraged that the news of an increased probability of funding may well attract additional applications.

In terms of quality, NCI staff believe, as indicated in the new NCI bypass budget, that increased funding in the RPG pool out to a success rate of 1 in 3 would fund only promising research of major potential significance. In addition, the new accelerated executive review program for making funding decisions on exceptions places increased emphasis on the quality of the original submission. This paradigm should help focus investigators on submitting better original applications to

maximize their chances for consideration, instead of expecting to submit one or more amended applications in response to advice from peer reviewers.

BROADCASTING CHANGE

Mr. Hoyer: What steps have you taken to inform other Institute Directors of the changes you have made at NCI?

Dr. Klausner: NCI funding initiatives have been presented in several venues across the NIH Campus. I personally described these activities at the regularly scheduled meetings of the NIH Institute Directors called by Dr. Varmus. Similar presentations have been made by NCI staff to the heads of the Extramural programs across the NIH. A publication entitled "Intramural Organization and Principles" was prepared by us which clearly describes the processes for resource allocation, recruitment, promotion and the prerogatives and responsibilities of the major types of positions within the intramural program. It also describes the review process by which the performance of Principal Investigators and Lab and Branch Chiefs will be judged. In addition, the new programs have been discussed at public meetings of the National Cancer Advisory Board, the Presidentially appointed advisory council of the NCI, and have been promulgated by the scientific press.

IMPACT ON OTHER INSTITUTES

Mr. Hoyer: Are other Institutes following your lead?

Dr. Klausner: Paylines have in general risen this year across NIH, with investigator initiated research being a stated priority, and the expedited Shannon Award program initiated by NCI is slated to be expanded in the coming fiscal year to all Institutes. NIEHS and NIMH have also begun comprehensive external reviews of their intramural programs similar to the Bishop-Calabresi Committee review that launched NCI's reform of its intramural programs, with other ICDs slated to follow. Dr. Varmus has indicated that through Dr. Wendy Baldwin's office, the NIH Office of Extramural Research, other ICD's have been given general advice concerning, among other areas, accelerated reviews and the concept of bridge grant funding. However, all of the changes must still be responsive to the tenets of the peer review system.

NEW AVENUES OF BREAST CANCER RESEARCH

Mr. Lowey: In your oral testimony, you noted that researchers are motivated by scientific opportunities to seek NIH funding. Can you discuss what scientific opportunities exist in breast cancer research that NCI might fund if it had additional resources?

Dr. Klausner: Recent changes and developments in molecular biology have opened extraordinary avenues for research advancement to understand breast cancer, its causes, prevention, and cure. New technological breakthroughs offer the capability to identify the genetic components of this disease, and to design new diagnostic, screening, chemoprevention, and therapeutic tools based on this growing knowledge.

A number of newly created opportunities exist for studying the interaction of genetic and environmental risk factors. The discovery within the last several years of two major genes, BRCA1 and BRCA2, related directly to breast cancer risk has greatly expanded our knowledge in understanding genetic mechanisms of this malignancy. However, in addition to these single genes, there are a number of relatively common susceptibility genes that may influence risk, and which are involved in the metabolism of endogenous (e.g., hormones) and exogenous (e.g., environmental) factors. The study of the joint effects of these genetically controlled susceptibility processes and various environmental exposures could greatly enhance our understanding of their interactive role in the etiology of breast cancer.

An additional area for new research opportunities involves further studies to clarify the role of hormonal factors in the etiology of breast cancer. Although it has long been recognized that breast cancer is influenced by hormonal factors -- as evidenced by high rates of disease in women with early menarche, late ages at first childbirth, and late ages at menopause -- how they relate to specific endogenous hormonal patterns remains unclear. Advances in the measurement of a number of endogenous hormonal markers greatly expands our ability to clarify biologic mechanisms underlying the disease. In addition, recent evidence indicates that hormones other than estrogens and progesterone, such as androgens, insulin and cortisol, may play an important role in the etiology of breast cancer.

Further research needs to be done into the development and validation of biomarkers that reflect cellular/tissue changes preceding malignant transformation. Evaluation of prognosis and survival utilizing clinical and biological markers, particularly related to individual susceptibility factors for breast cancer is another area in need of additional research. Opportunities also include research into second malignancies developing after breast cancer diagnosis and treatment, small grants for technology transfer in breast cancer research and training grants for interdisciplinary training in the genetic epidemiology of breast and other cancers.

Recent success in elucidating the components involved in the control of cellular proliferation and the surveillance of the integrity of genetic information have identified likely targets for cancer-causing events. Some of these components have already been shown to be particularly relevant to breast biology and breast cancer. For example, cyclin D1 -- a protein critical in initiating cell proliferation -- is required for the normal epithelial cell proliferation associated with lactation but too much of this protein can lead to breast cancer in animal models. Although reproductive hormones are assumed to play a direct role in these cellular events, the connection between the two is currently unknown. A new research emphasis on the convergence of endocrinology and basic cell biology could provide important information about breast cancer in vivo.

There are extraordinary opportunities in a variety of research areas which directly impact our understanding of the genesis and treatment of breast cancer. Additional resources would provide the opportunity for NCI to fund research related to identifying additional genes which predispose individuals to breast cancer. Several, but not all, breast cancer susceptibility genes are known. The chromosomal locations of genes thought to be involved in breast cancer have been identified. Determining the genes contained within these genomic regions has proven extremely valuable in the past for discovering breast cancer markers and will be equally important for identifying additional markers.

Within the Human Genome there are 22 areas that have been identified to be regions prone to loss of heterozygosity (LOH). Within three of these LOH regions, three genes have been isolated which are directly involved in carcinogenesis, BRCA-1 is one of the genes. A large effort toward characterizing the 22 genetic regions fully to search for genes involved in cancer progression is possible. Funding could be targeted toward breast cancer studies but the result will probably be the discovery of genes that are involved in many forms of human cancers.

The effort involved in studying LOH regions is more an issue of increased manpower and funding and not one of technology. The current technology is adequate to genetically characterize these regions.

Research is needed in developing animal models for human breast cancer to allow testing of new therapies and the study of genetic interactions and environmental effects on mammary oncogenesis. The development of genetic knock-out animal models could allow testing of key genetic pathways and protein interactions.

An area of additional research involves studying the basic biology of mammary development and differentiation and carcinogenesis. During the development of cancer, many cellular controls which regulate normal cell growth and differentiation are lost. Understanding how the normal cellular controls function during mammary development will provide new avenues to analyze the process of the growth of tumor cells. Increasing basic research of mammary genesis projects,

specifically in the areas of gene expression, gene function, cell cycle regulation, signal transduction and regulation of differentiation as they impact on normal development and the development of cancer, is essential.

Opportunities are available for additional research efforts in developing new diagnostic techniques and instrumentation for identifying at-risk individuals.

Multiple outstanding scientific opportunities exist for funding breast cancer research related to prevention and early detection in women at risk for developing breast cancer. The Community Clinical Oncology Program (CCOP) network will be an important part of national programs for control and intervention research. Specific areas for research include development of early detection methodology that reflects an improvement over conventional mammography using markers of premalignant disease and methods that enhance its detectability. This increased understanding of breast cancer biology and identification of women at risk will require new breast cancer prevention initiatives including clinical trials. Once demonstrated in high risk women, it is anticipated that some breakthroughs can be generalized to women who are at risk for developing breast cancer even though they do not have known risk factors.

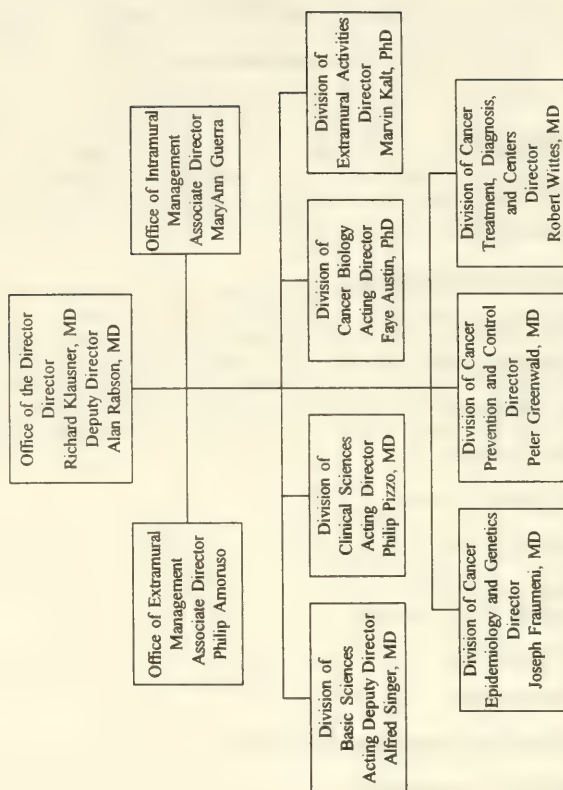
Research aimed at studying the effects of modifier genes and environmental cofactors on oncogenesis in individuals carrying susceptibility genes is another area of opportunity. Although many individuals inherit susceptibility genes, not all individuals with these genes develop cancer. This difference is due to differences in genetic backgrounds and specific environmental factors. Identifying modifier genes will improve our ability to define risk groups with greater certainty. Current technology exists for this effort although new and improved techniques could expedite discovery.

JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

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NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Organization Structure

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV (except Section 417B(d)) of the Public Health Service Act with respect to cancer, \$2,060,392,000.

A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$1,919,419,000	\$2,251,084,000	\$2,060,392,000
Reduction in accordance with PL 103-333.....	-2,499,000		
Rescission in accordance with PL 104-19.....	-3,101,000		
Subtotal, adjusted appropriation.....	1,913,819,000	2,251,084,000	2,060,392,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-1,636,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV Activities.....		-225,790,000	
Comparative transfer from: Other NIH Institutes for Management Fund Adjustment.....	984,000		
Subtotal adjusted budget authority.....	1,913,167,000	2,025,294,000	2,060,392,000
Unobligated balance lapsing.....	-244,000	---	---
Total Obligations.....	1,912,923,000	2,025,294,000	2,060,392,000

¹ Excludes the following amounts for reimbursable activities carried out under this account: 1995 -- \$15,795,000; 1996 -- \$20,000,000 and 1997 -- \$20,000,000.

Also excludes funding for HIV activities: FY 1996 -- \$225,790,000; FY 1997 -- \$220,539,000, included in the Office of AIDS Research, NIH.

Note: Excludes \$12,765,000 for royalties in FY 1995 and \$13,500,000 in FY 1996.

Justification

National Cancer Institute

FY 1995		FY 1996		FY 1997		Increase or Decrease	
Actual		Estimate		Estimate			
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2231	\$1,913,167,000	2187	\$2,025,294,000	2187	\$2,060,392,000	---	\$35,098,000

This document provides justification for the FY 1997 non-AIDS activities of the National Cancer Institute (NCI). Justification of the NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction:

"A world without science is a world without hope" - Peter Medawar

"The main object of all science is the freedom and happiness of man" - Thomas Jefferson

Twenty-five years of government support for cancer research has provided both wonder and heartache. The wonder has come both from our success in treating certain tumors and from our astonishing new knowledge of how cancer cells work. These advances have been heartening, and they herald great promise for the future. The heartache comes from what we haven't been able to do. Our understanding of cancer's complexities remains incomplete, frustrating our fervent desire to eradicate this scourge once and for all. Through 25 years of tireless and exacting science, we have made great strides against cancer, but there is still much to learn, much to do.

How do we continue to move forward? Part of the answer is to sustain proven research programs that have brought us to this juncture. At the same time, we must recognize and seize the extraordinary opportunities for further progress earned through our national investment and our diligence. We have built a successful discovery process, attracted some of the best scientific minds to the cancer problem, and initiated ground-breaking programs that already have yielded critical knowledge, improved patient care, and saved lives. We must continue to support these endeavors, ensuring that they remain vital and productive.

A rare disease at the turn of the century, cancer is all too commonplace today. This budget represents an investment in research, but more importantly an investment to improve the Nation's health. Most importantly, it is an investment in hope--the hope that springs from the discovery of the tools and knowledge that we must have to reduce the awful burden of cancer.

Over 40 percent of us will develop cancer; over 20 percent of us will die from cancer. Within five years cancer will be the leading cause of death in the United States, responsible for over 6 million years of life prematurely lost each year and an annual cost to the economy of over \$100 billion.

The National Cancer Institute (NCI)—An institution dedicated to discovery

The NCI is the core of this Nation's response to the scourge of cancer. Science is the way we understand the natural world and the NCI is an institution of science dedicated to discovery about all aspects of cancer. Its work is based on the premise that we must know what causes cancer in order to prevent it and we must know the nature of cancer in order to accurately detect, diagnose, and treat it.

Research is the process by which questions about cancer are asked and answered. These key questions include:

- | | |
|-------------------|---|
| • Cancer Risk: | Who is at risk for which cancers and why? |
| • Prevention: | How can cancer be prevented? |
| • Detection: | How do we screen for, detect, and diagnose cancer? |
| • Treatment: | How do we best treat cancer? |
| • Rehabilitation: | How do we improve quality of life for cancer survivors? |

While we have made progress in answering these questions, the burden of cancer continues.

Progress Against Cancer

We measure progress against cancer in terms of:

- The growth of knowledge about cancer; and
- Reductions in the cancer burden.

The growth in knowledge: Twenty-five years ago three theories of cancer (one based on viral causes, one based on heredity, and a third based on chemical causes) dominated cancer research, but there was little direct evidence for any of these theories for the vast majority of human cancer. All of that has changed with the discovery of two classes of genes, oncogenes and tumor suppressor genes. The first was discovered through the study of viral cancers in animals, the second through the study of hereditary cancers in humans. The present view of cancer has emerged from a fusion of all three hypotheses. Cancer is a disease of altered genes and altered gene function. These alterations can be inherited or acquired as the result of chemical or physical damage or the effects of viruses.

What is cancer? Today we know that cancer results from a series of changes in genes that control cell growth and behavior. These genetic changes transform a healthy cell, or one that has inherited a predisposition to these changes, into a cancer cell. One of the critical questions in cancer research is how and why these genetic errors occur, and just as important, why the errors are not corrected by the cell's normally efficient surveillance mechanisms. The relationship of these genetic changes to the environment, and to behaviors such as diet and smoking, is especially important. Smoking is the cause of over 30 percent of cancer deaths and diet may be implicated in an even greater number of cancers. Cancer is a group of diseases whose origins lie in the interplay between the vulnerability of our genetic material, DNA, and the challenges and stresses that environment places on the cells in which DNA is housed.

These new developments in our understanding of cancer are extending to all forms of human cancer. At first, the genetic basis of cancer was observed in certain rare cancers but now these insights are extending to the most common cancers. Genes whose dysfunction accounts for cancer are being rapidly identified. These genes ultimately determine the behavior and the relentless growth of cancer cells. Some of these genes, the oncogenes, can be activated inappropriately, similar to the uncontrolled accelerator of an automobile. Conversely, the tumor suppressor genes, or anti-oncogenes, can lose their function, like defective automobile brakes. Our knowledge about these genes is still incomplete, and many cancer genes remain to be found. Ideas abound on ways to use the new information for cancer prevention, diagnosis, prognosis, detection, and treatment. In short, the whole field of cancer research has been revolutionized and energized by this recent and continuing genetic revolution.

Reducing the burden—the NCI's ultimate goal: Reducing the burden of cancer can be measured in terms of fewer deaths, fewer new cases, increased length of survival, and increased quality of life of cancer survivors.

For several cancers, decreasing death rates reflect cumulative research successes over the past 25 years: death rates from children's cancers have declined by over 50 percent, and with advances in chemotherapy, hormonal treatments, and in the access to and use of screening mammography, breast cancer mortality has finally begun to decline—down five percent since 1989. Deaths from colon and rectal cancers have dropped steadily, declining 10 percent in the past 25 years, and mortality rates have also decreased for Hodgkin's disease and testicular cancer, both due to dramatic advances in therapy.

After a formidable battle to reduce the prevalence of cigarette smoking, lung cancer rates for men have declined. As smoking rates among women have increased, however, their lung cancer mortality rates have risen alarmingly. For other cancers, including non-Hodgkin's lymphomas, melanoma, brain, kidney, pancreas, and prostate cancers, mortality rates have not fallen or are increasing. Particularly disturbing are African Americans' higher mortality rates for many cancers.

In addition to improvements in mortality rates for many malignancies, we have achieved important improvements in the quality of life for cancer survivors through less disfiguring and less damaging surgical procedures, better pain control, and more effective medication for the side effects of cancer therapy.

Yet, even taking into account the advances, overall cancer incidence continues to increase, emphasizing the formidable task ahead. The goal of a reduced cancer burden can only be achieved by the successful translation of discoveries to the benefit of people, all people, who are at risk for and who have cancer.

NCI Research Program

The National Cancer Institute research program is illustrated schematically in Figure 1.

Research Venues: The research programs of the NCI take place in three venues: the laboratory, the clinic, and the community. In the laboratory, research is pursued on the biology of cancer, the fundamental properties of cancer-causing agents and processes, and the body's defense against and response to cancer. In the clinic, patient-oriented research is carried out concerning prevention, detection, diagnosis, treatment, and rehabilitation. In the community, research is carried out on the causes, risks, predispositions, incidence, and behavioral aspects of cancer. As the diagram indicates, the components of this research triad overlap. For example:

Population or community-based research on the effects of exposure to a potential cancer-causing agent links to the laboratory where an understanding of the agent's effect on the cell can be explored. Through these linkages, we have identified a sexually transmitted papilloma virus as the cause of cervical cancer and subsequently explained why only certain viral sub-types are cancer causing; and we have established the relationship between asbestos and mesotheliomas; between late menopause and breast cancer; and between diet and esophageal or stomach cancer.

Likewise, community-based research on family clusters of cancers can lead to the isolation of the specific genes responsible for inherited cancer syndromes. The identification of specific genetic pathways in cells studied in the laboratory then can be applied to patients in order to predict the course of their disease and their response to therapeutic interventions, or to find ways to detect these cancers very early in their development.

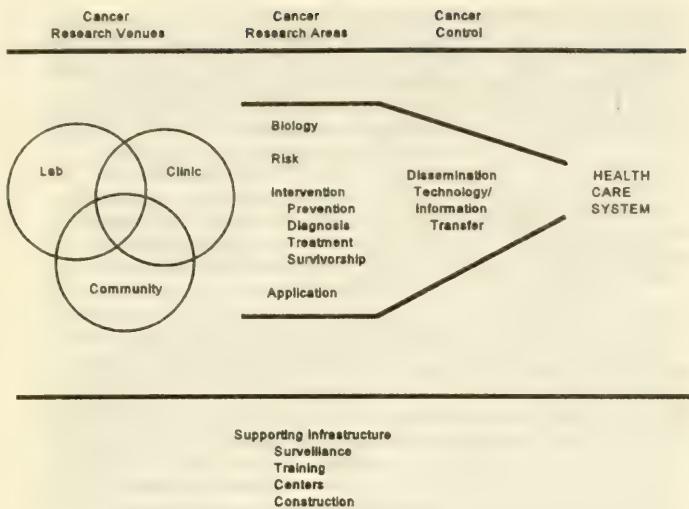


Figure 1

Figure 1 shows a progression from the results of research through dissemination to application. Research results must be communicated to those who ultimately apply these results in health care and disease prevention settings, and this communication process is an important part of the NCI infrastructure.

Research Areas: There are three fundamental cancer research areas--in effect three fundamental goals of cancer research: An understanding of cancer biology; identifying who is at risk for cancer and why; and developing interventions to prevent, detect, diagnose, treat, and enhance survivorship from cancer.

Cancer Biology - The Nature of Cancer: The most remarkable progress in the last 25 years has been in our knowledge of cancer biology. We are finally beginning to understand what is required to turn a normal cell into a cancer cell. Cancer arises when a single cell changes so that it divides continuously, released from the controls that constrain the replication of normal cells. In all cases this transformation is due to changes in the function and activity of genes. Genes are

segments of DNA containing the information that directs a cell to make a particular protein product. Of the 100,000 genes found in the human genome, only the altered activities of a small number of genes are responsible for transforming a normal, well-behaved cell -- be it in the breast, brain, blood, colon, prostate or other organ -- into a cancer cell. Identifying these "cancer genes" defines the central scientific hunt in cancer biology. Their identification provides an unprecedented window onto the nature of cancer. These genes normally function to instruct cells to produce accelerators that drive cells to proliferate, brakes that control proliferation, or mechanisms that underlie the repair of DNA damage or the sacrifice of damaged cells. Some individuals inherit an altered form of a cancer gene. These individuals carry a very high lifetime risk of developing cancer because fewer subsequent changes in DNA are required to take place in one of the trillions of cells in our bodies to transform that cell to a cancer cell.

We now know that DNA changes are the core cause of all cancer. These changes can occur due to chemicals, viruses, radiation, and mistakes made each day in the course of duplicating the three billion units in our DNA when a cell divides. DNA, the molecule of life, is very vulnerable to damage, but each cell has the remarkable ability to recognize damage and correct it. The changes in DNA required to produce cancer result from the imbalance between damage and the cell's ability to repair the damage. When a normal cell recognizes damage to its DNA, it stops the process of growth and division called the cell cycle. A normal cell either repairs the damage or, if it fails, commits suicide. In the development of cancer these "checkpoint" controls are lost and the cell continues to divide, transmitting its damaged DNA to its descendants. It is for this reason that cancer is beginning to be seen as a problem of genetic instability.

No one genetic alteration, however, is enough to make a normal, healthy cell a cancer cell. Rather it is an accumulation of changes during the lifetime of a cell in a relatively small number of genes that is required. This understanding allows us to begin to define the development and evolution of cancer from predisposition to pre-cancer to cancer. Each cancer is ultimately defined by its particular pattern of altered and normal gene activity. This pattern determines the cancer's rate of growth, tendency to spread, responsiveness to hormones and therapies, and defines the ability of a person's immune system to recognize and respond to a cancer. It is these patterns that will define what each cancer is and how many different cancers there are.

By defining these molecular patterns we are beginning to be able to describe what distinguishes each cancer from its normal counterpart. Advances in our ability to detect, to diagnose, and to treat each cancer will most likely be found in these differences.

Cancer Risk: Research on cancer risk quantifies the risk of developing cancer in various populations, and strives to identify the factors responsible for these risks. Research in this area is critical to linking our knowledge of biological processes to the detection, management, and ultimately, prevention of cancer. Studying people who are at high risk of cancer is particularly important, since it may be possible to more readily identify the factors influencing risk and to assess means for prevention and risk reduction.

Epidemiology is the principal discipline used to study cancer patterns in the population and the determinants of cancer risk. Epidemiologists have uncovered distinct cancer patterns among various population groups. For example, African American men have the highest prostate cancer risk of any group in the world, while men in Asian countries have a relatively low risk. Similarly, women in Asian countries have the lowest rates of breast cancer, while those in the West have the highest. Interestingly, when Asian women migrate to the United States, their breast cancer risk rises over several generations until it matches that found in U.S. white women. These striking variations among populations have proven particularly useful in targeting further epidemiologic research into the causes of cancer. These studies underlie the commitment of the NCI to address the burden of cancer in all groups in our American community to assure that all groups receive the benefits of our research.

The epidemiologic approach has been successful in identifying many factors that increase cancer risk, some of which are environmental and lifestyle-related, while others are part of a person's genetic makeup. With the exception of a few genetic conditions, however, it is still not possible to predict with any degree of certainty that a person having one or more of these factors will develop cancer. This uncertainty is related to the very nature of cancer, and the need for a number of specific alterations to accumulate in the genetic material (DNA) of a single cell for that normal cell to be transformed to a malignant state.

The single most important exposure that increases cancer risk is the use of tobacco products, particularly cigarette smoking. Smoking is believed to contribute to more than 30 percent of all cancer deaths. In addition, certain aspects of the diet, particularly diets lacking in fruits and vegetables or high in fats, appear to be important contributors to cancer risk. An excess risk of cancer also has been linked to alcohol consumption, radiation (e.g., ultraviolet and x-rays), certain occupational exposures (e.g., asbestos), environmental pollution (e.g., inorganic arsenic), some pharmaceutical agents (e.g., estrogenic drugs), certain viral infections (e.g., human immunodeficiency virus--HIV and human papilloma virus--HPV), and hormonal factors. In addition, epidemiology plays a key role in revealing inherited cancer predisposition syndromes, as is seen in women who inherit alterations in the BRCA1 gene.

With recent major advances in molecular biology, a strategy called molecular epidemiology has emerged, combining the strengths of epidemiology with sensitive laboratory probes and providing new insights into genetic susceptibility and gene-environment interactions. This kind of interdisciplinary approach promises to elucidate the risk profiles and biologic mechanisms involved in cancer etiology, making it possible to predict cancer risk with greater certainty.

My dad died of colon cancer; so did his mother. My uncle got it when he was 48. My sister has ovarian cancer. I'm 44 and my son is twelve—of course I wonder if I'm next, but I worry the most about his future.

The most common form of inherited colon cancer—hereditary nonpolyposis colorectal cancer, or HNPCC—may be responsible for one in six colon cancers. Over a million Americans may carry one of four mutated genes known to be involved in HNPCC. People with a defective gene face about an 80 percent chance of developing colon cancer, usually before age 50. HNPCC carriers also have higher risks for stomach and kidney cancers, and women have higher risks for ovarian and uterine cancers.

Since 1913, we scientists have suspected a genetic connection in families with an unusually high incidence of cancer. Not until 1993 did researchers have the tools to move from observations to the unequivocal identification of culprit genes. Now we have the knowledge and the tools to move quickly toward replacing genes or repairing genetic defects. This was science fiction only 10 years ago. The pace of discovery will accelerate from now on.

In HNPCC, the gene mutations cause a breakdown in the system that corrects DNA duplication errors during cell division. Over time, uncorrected errors in other key genes allow cancers to develop at an accelerated pace. This is a primary cause of cancer—a pathway that enables a cell to evolve quickly from a normal cell to a cancerous one. HNPCC cancer cells also seem able to resist normal signals to stop dividing or die. The same problems have been found in cancers that do not appear to be inherited, which means that knowledge gained from HNPCC research may be relevant to many other cancers.

Now we need to focus on the biological basis of these genetic changes and learn how interactions with other genes and with environmental factors influence which HNPCC gene carriers develop cancer. Then we can find ways to keep those at high-risk from developing malignancies. We have to learn how best to screen and counsel people about their cancer risk, and we must address the important medical, social, ethical, and legal issues that come with genetic knowledge.

I will be tested. I'll let my son decide for himself when he's older. We are doing what we can to minimize the risk by eating a high fiber-low fat diet. I'm very encouraged by the research. By the time my son might get cancer, I think they'll know how to turn these genes off or reverse their effects. I want this sword lifted from over my family's head.

Cancer Interventions: Ultimately, the purpose of understanding tumor biology is to discover more effective ways of preventing, diagnosing, and treating cancer. Although the full realization of this process lies ahead, important advances achieved over the past quarter-century give ample reason for optimism.

The diagnosis of cancer depends on the microscopic appearance of tissue samples taken from growths or other suspicious lesions in the body. Advances in biological knowledge have improved our ability to subclassify cancers into accurate categories. For example, a better understanding of normal immune system development and biology has led directly to molecular techniques for classifying, for the first time, immune system tumors (lymphomas). Better classification of cancers is important because it will lead to more precise prediction of clinical outcome for patients and to the discovery of more effective therapy. The experience with lymphoma serves as a model for what will very likely occur in a variety of malignancies. We expect that tumor diagnosis and classification will be revolutionized in the coming years by application of emerging knowledge in molecular genetics.

We have learned to see inside the body of living human beings with a precision that could not have been anticipated by a previous generation of physicians. Computed tomography, magnetic resonance imaging, and ultrasonography simply did not exist as useful clinical tools 25 years ago. Their development depended on first learning how the body interacts with X-rays, magnetic fields, and sound waves, and then figuring out how to create images from these interactions. These technologies permit us to locate internal tumors with unprecedented accuracy, and to biopsy internal organs without the need for major surgical procedures. There is every reason to believe that further improvement in their powers of resolution will enhance our ability to detect small tumors even earlier than is possible with currently available methods, such as X-ray mammography. Invasive procedures, such as colonoscopy and bronchoscopy, are on the verge of giving way to "virtual" procedures involving the imaging of these internal structures without any actual invasion of the body by tubes or scopes.

Our ability to prevent cancer depends on identifying and removing (or at least reversing the effects of) specific risk factors. Clearly, the most important of these is tobacco use. The NCI has strongly supported recent initiatives to avert the initiation of tobacco use among children and teenagers and continues to develop a variety of approaches to cessation

among those already addicted. The effect of dietary modification and administration of preventive agents to forestall the occurrence of cancer in high-risk populations is currently under study. The testing of tamoxifen as a breast cancer preventive is one current approach. It should be quite clear, however, that major improvements in our approach to chemoprevention will depend on an improved understanding of the fundamental mechanisms of carcinogenesis -- the process by which normal cells are induced to become malignant.

The past quarter century has seen major progress in our ability to treat certain cancers. In addition to well-publicized improvements in the cure rates for many uncommon tumors, such as Hodgkin's disease, certain lymphomas, testicular cancer, and a variety of childhood cancers, adding chemotherapy to surgery and/or radiation has increased the cure rates for patients with breast and colorectal cancer. High-dose chemotherapy with stem-cell rescue is effective in the leukemias and is currently undergoing definitive testing in breast cancer. The application of molecular biology to the drug discovery process has ushered in the era of biological therapy by permitting the large-scale production of so-called "recombinant" proteins. Following directly from this approach, the availability of interferon-alpha has markedly improved the outlook for patients with a rare form of leukemia. Both interferon and interleukin-2 provide improved palliation for some patients with kidney cancer. The availability of bone-marrow stimulatory factors have enhanced the quality of supportive care by mitigating the toxicity of chemotherapy to the blood elements. Over the past 15 years, the formidable problem of treatment-related nausea and vomiting has been markedly lessened by the development of truly effective drugs that block this side effect.

NCI is committed to research to improve the quality of life for those who develop cancer. As treatment becomes increasingly effective in the coming years we shall continue to see the emergence of certain problems associated with surviving cancer. These are of two general types. The first are the challenges to an optimal quality of life posed by the effects of cancer treatment itself. Although most acute side effects of treatment are rapidly reversible, some, such as the loss of a body part, have a lasting impact. The widespread use of techniques such as breast reconstruction, conservative surgery, and customized limb prostheses have greatly improved the emotional and functional outlook for survivors of breast and bone cancer. The knowledge, gained in a landmark clinical trial, that chemotherapy followed by radiation treatment is as effective as total removal of the voicebox for cancer of the larynx has made preservation of natural speech possible for many patients with this condition. The recent FDA approval of effective drugs for protecting against the cardiac toxicity of the anthracycline antibiotics and the kidney toxicity of cisplatin can be expected to reduce the overall incidence of two particularly troublesome chronic effects of treatment.

The second general problem is the propensity of many cancer survivors to develop second cancers at the same or other body sites. In some cases, this too is a treatment effect, since many current therapies that effectively treat the patient's primary cancer unfortunately promote the

development of second cancers in a small fraction of people who receive them. So, for example, women who have received radiation therapy to the chest for the treatment of Hodgkin's disease are at increased risk for developing breast cancer; and certain chemotherapy regimens are associated with the late appearance of acute leukemia in some patients who survive for years after the treatment. Sometimes, however, the development of a second cancer stems from influences having nothing to do with the therapy. For example, patients who survive a first cancer of the lung or oral cavity, for instance, have a high incidence of subsequent tumors at those sites, probably because of the continued carcinogenic influences of tobacco. Inherited risk may also play a role. Some breast, ovarian, and colorectal cancer patients have a genetic predisposition to those cancers and are likely to develop second primary cancers. The solution to these persistent problems is clearly to discover more targeted and less toxic treatments and to develop better surveillance and prevention strategies for people whose risk is elevated for reasons unrelated to treatment.

Psychosocial and behavioral research has fundamental contributions to make to all aspects of cancer survivorship, both in improving the quality of life for cancer patients as well as and those at increased risk of developing cancer. In this area, psychosocial research investigates how cancer affects quality of life and finds ways to address survivors' needs so they can meet the everyday demands of life and return to a productive lifestyle. NCI is committed to such research to complement its cancer prevention, detection, and treatment research programs. We expect that this research will assume even greater importance as genetic advances pose difficult prevention and treatment choices.

Cancer Control

Cancer control refers to the application of cancer research results and interventions to decrease the burden of cancer. Just as biology and epidemiology provide a foundation for intervention research, all three research venues provide a foundation for cancer control. The fact that significant smoking rate reductions have taken over thirty years to achieve since the first Surgeon General's Report which linked smoking causally with cancer, demonstrates how difficult the widespread application of cancer research results can be.

Each year, over 500,000 Americans die of cancer, while over 1,000,000 are newly diagnosed. Clearly, knowledge gained in the biological and epidemiologic sciences as well as that gained in intervention research must be broadly applied to have an impact on the cancer problem in the United States. Effective applications rely upon rigorous, high quality science. Just as important, effective applications require an in-depth understanding of and sensitivity to the cultural, ethnic, and other social forces acting upon populations. Behavioral research on why teenagers take up smoking, on the kinds of foods eaten and not eaten by different social groups, and research on the attitudes and beliefs Americans hold about preventive screening and therapeutic medical practices all play an important role in cancer control. Ultimately, cancer control will involve behavioral changes, both in the behavior of health professionals as they carry out their medical and public health practices and in the behavior of the American people in their everyday lives. Effective

cancer control requires attention to careful assessments of the nature of scientific evidence necessary for technology transfer from the laboratory to the clinic, public health department, and community. Effective cancer control also involves the highest standards of ethical conduct, not only in the conduct of science, but in terms of the social and ethnic mores of the uniquely diverse American society. Health professionals carry an important obligation to protect the public health through effective and appropriate interventions. The public, in turn, has a right to know about the nature of cancer research using human subjects and a right to know which treatments and preventive and early detection interventions are judged to be the best, given the scientific knowledge of the day.

NCI also supports a national demonstration project, called American Stop Smoking Intervention Study for Cancer Prevention (ASSIST), which tests tobacco use interventions to determine what mix of education, community involvement, media messages, smoking cessation help, and policy change will best keep our children and other high risk populations from smoking. This program represents a collaborative effort between the NCI, the American Cancer Society, State and local health departments and other voluntary organizations to develop comprehensive tobacco control programs in 17 states and metropolitan areas.

It follows that a central effort in applying the knowledge gained in biology, epidemiology, and intervention research involves effective and widespread communication. The NCI maintains several important lines of communication. Our scientific journal, the *Journal of the National Cancer Institute* (JNCI), is now the premier cancer journal in the world. Although designed primarily to facilitate communication between scientists and clinicians, the JNCI is often cited in the popular press and therefore is an important channel for public information. The NCI also supports communications between scientists, physicians, and the public through its nationwide Cancer Information Service (1-800-4-CANCER) and the PDQ computer-based cancer and clinical trials information system. These communication systems provide Americans--physicians, patients and the public--with the most current information possible on cancer treatments and on effective early detection, supportive care, and prevention technologies.

Cancer control is the final step in carrying out the basic mission of the NCI: to understand the nature of cancer and to apply that knowledge to reduce the burden of cancer--the deaths and disabilities--so that all Americans can lead healthier and longer lives.

Key Changes in Organization:

Reorganization and Management Improvement to Maximize Progress-Streamlining

The mission of the NCI is scientific discovery about all aspects of cancer toward the ultimate elimination of cancer from our lives. As our understanding of cancer has grown and our capacity to attack it has blossomed, NCI has recognized a need to re-examine and revise its organizational structure to ensure a cohesive, efficient approach to the myriad initiatives and programs the Institute brings to bear on the cancer problem.

The new NCI leadership initiated a major reorganization and significant management improvements, based on recommendations of the Ad Hoc Working Group of the National Cancer Advisory Board and NCI streamlining workgroups and quality improvement teams. These changes, including decentralized authority for many operating decisions, reflect NCI's recognition that programmatic and cost efficiencies were both possible and would best realize the Institute's mission by enhancing scientific program management, reducing duplication and overlap, fostering a uniform standard of intramural research excellence, improving communication between scientists working in related areas, improving and simplifying administrative functions, and optimizing the use of information technologies.

To achieve these efficiencies and better align the organization's structure with evolving scientific priorities, the extramural programs have been regrouped to reflect current scientific knowledge and co-locate certain clinical grant programs for more efficient scientific management. All intramural laboratory, clinical, and population-based research has been consolidated under three new divisions. The Office of the Director has been restructured and includes the Offices of Strategic Planning and Technology Development to ensure continuing surveillance of opportunities to improve planning, management, and efficiency.

Moreover, the reorganization makes real NCI's dedication to stronger participation in decision-making by the cancer research community while at the same time streamlining the advisory committee structure. A single Board of Scientific Counselors (BSC), reviewing and advising on intramural research, replaces the four Boards previously addressing activities of each of the four program divisions. Similarly, one Board of Scientific Advisors (BSA) will appraise and make recommendations for the extramural programs. And for the first time both Boards now include members of the lay community in addition to leading scientists. Advisors will now be able to consider the programs of the NCI as a whole, rather than only the type of science funded by a single division.

Steps have also been taken to solicit advice from the community of NCI intramural scientists and the scientific and administrative staff responsible for the review, award, and scientific management of the grant programs. The internal Intramural Advisory Board (IAB) and Extramural Advisory Board (EAB) meet regularly to advise on policy and process and serve as information conduits back to the staffs they represent.

The NCI Executive Committee, which meets weekly to make major policy and operating decisions for the institute, has been newly reconstituted to include the chairs of the IAB, EAB, BSC, and BSA. In this way, the extramural community and the internal working scientists and scientific administrators inform and influence key NCI policies and actions.

How NCI Works

The most important component of the National Cancer Institute research program is investigator-initiated research. It is the life-blood of science and the cornerstone of the National Cancer

Institute. Over one-half of the Institute's budget is devoted to such research, which is funded under a variety of peer-reviewed grant mechanisms designed to optimize the purpose of the research and the likelihood of project success. There are mechanisms focused on single projects undertaken by single investigators; on Program Projects that enable a team of investigators to develop a group of related projects, which by being carried out together will achieve more than if each was carried out singly; on First awards for new investigators to enable them to develop a rapid foothold in science; and on small business and industry-academic collaborators.

Peer-review is fundamental to investigator-initiated research. A grant proposal/application submitted to the NCI is reviewed by one of over 100 committees (termed study sections or peer-review groups) composed of scientists in fields closely related to the applicant's research. The peer-reviewers give each grant a score reflecting the importance of the topic proposed, the rigor of the study design, and the investigator's ability to achieve the aims of the research. With the assistance of its principal advisory body, the presidentially-appointed National Cancer Advisory Board, the NCI examines each of the grants submitted, weighs the evaluation of the peer review groups, then critically assesses cancer research priorities and its budget in order to make funding decisions.

To carry out research requires an extensive set of mechanisms, organizations, and networks linking researchers, facilities, and information. This infrastructure supports cancer research through diverse endeavors including developing central resources in tissue and data banking; conducting directed programs in drug discovery and large-scale screening for preventive agents, tracking changes in cancer incidence, mortality and morbidity; and fostering the critically needed training of cancer researchers.

Like investigator-initiated research, most components of the infrastructure are funded through grants and evaluated through peer-review, including a network of Cancer Centers, Community Clinical Oncology Programs, and Clinical Trials Cooperative Groups. Other components are funded under contract, such as the Surveillance, Epidemiology and End Results Program, a network of cancer registries providing surveillance information on cancer incidence, mortality, and survival. The NCI's Frederick Cancer Research and Development Center is also funded under contract, and all contracts are evaluated through a peer-review mechanism.

The purpose of research is to develop understanding. NCI's cancer research funding strategy is to assure that there is sufficient funding to enable scientists to pursue those research areas with the greatest scientific opportunity—that is, the greatest opportunity to increase our knowledge of cancer. As we have noted, research on cancer involves the full spectrum of research, from the most fundamental laboratory research, to large scale trials of cancer prevention and treatment methods. Funding decisions are based principally on the advice of scientists themselves as to those areas and projects that have the greatest potential to expand our knowledge of cancer. This expansion can occur in ways that at first may seem unlikely. For example, research on families who seem to have a propensity to develop breast cancer has shown they also have a higher risk of prostate cancer, linking both to the same gene. Similarly, research on the viral causes of cancer

led to the identification of the gene p53, now understood to be a tumor suppressor gene that fights the development of almost all cancers.

A second critical factor in our funding strategy, in addition to scientific opportunity, is the burden of specific cancers. For example, breast cancer, the leading cancer among women with over 180,000 new cases each year, is a major priority for NCI as reflected by the FY1995 funding directly related to breast cancer of about \$315 million. Funding for prostate cancer the leading cancer among men, and in fact the single cancer with the greatest number of new cases each year--over 300,000--amounts to about \$60 million. Both these amounts represent resource allocations consistent with research opportunity. It is important to realize, however, that research on the hormonal aspects of testicular cancer, a relatively rare cancer with about 7,000 cases annually, may well provide clues to these cancers as well. There is no research allocation schema that can account for these inter-relationships between cancers, nor between fundamental and applied research. Advances against one type of cancer may well affect every other type of cancer. These advances come from non-targeted research that has the potential to apply the engine of discovery to all cancers.

Resources for Cancer Research: The NCI FY1997 Budget Request

This FY1997 President's Budget of \$2,060,392,000 represents an increase of \$35,098,000 over the FY1996 Continuing Resolution. Funds for NCI research activities in AIDS research are included in the NIH Office of AIDS Research (OAR) request. The President's Request assures that the multiple facets of the existing cancer research program are able to progress. Progress against cancer is contingent on a balanced program across laboratory research, research on risk, treatment, detection and prevention, and cancer control. Over the past year we have made many changes in organization and program to reach an appropriate balance. We have reduced intramural contract research levels and expanded the base of extramural research. A strong National Cancer Program must pursue these multiple strategies of research, maintaining a solid foundation and seizing opportunities for progress when they present themselves.

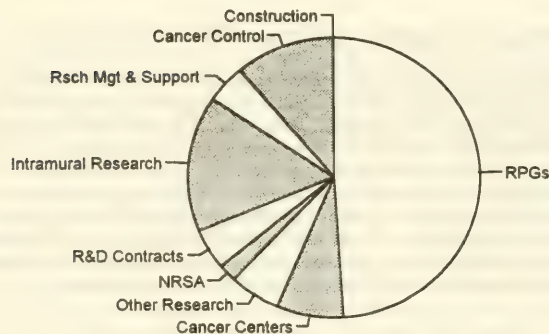
In 1971 Congress passed the National Cancer Act, increasing resources for cancer research and broadening the mandate of the National Cancer Institute, the principal Federal agency supporting and conducting cancer research. Today, some 25 years later we have made progress against many cancers, but the most profound change has been in our understanding of the fundamental biology of this constellation of diseases. It was the infusion of funds following the National Cancer Act that led to the genetic revolution in cancer and biomedicine in general. These funds spurred research on the leading causes of cancer and led to new treatments for children's cancers, colon cancer, Hodgkin's disease, testicular cancer, and breast cancer. Taxol® is one of many new anti-cancer drugs that can be directly attributed to this increased effort. These funds were instrumental in the development of the

biotechnology industry and in helping to fight diseases other than cancer. For example, the early study of retroviruses funded by the National Cancer Institute has been critical to advances in AIDS research and treatment.

We find ourselves with opportunities for investment in every facet of cancer research and the FY1997 Budget Request will permit the NCI to continue the support of research directed toward the further identification of causes, improved detection and diagnosis approaches, improved clinical treatment studies as well as basic, fundamental research. Activities in the prevention and control of cancer will be pursued as well.

FY 1997 Budget Request \$2,060,392*

Dollars by Mechanism
(in thousands of dollars)



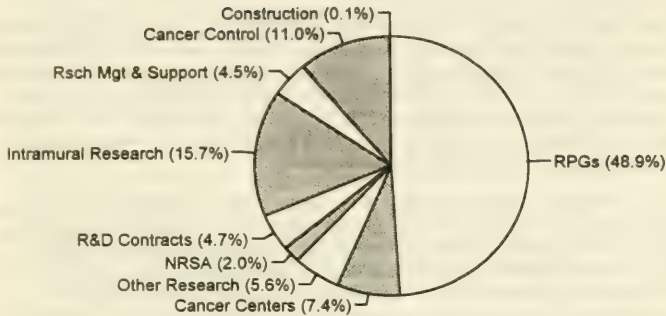
Research Project Grants (RPGs).....	\$1,008,451	Research & Development Contracts.....	\$96,153
Cancer Centers.....	152,447	Intramural Research.....	323,754
Other Research.....	115,799	Research Management & Support.....	92,129
National Research Service Awards.....	42,159	Cancer Control.....	227,500
		Construction.....	2,000

*Funds for NCI AIDS research are requested through the NIH Office of AIDS Research

Figure 2

FY 1997 Budget Request

Mechanism by Percent of Total



Mechanism by Percent

Research Project Grants (RPGs).....	48.9%	Research & Development Contracts.....	4.7%
Cancer Centers.....	7.4%	Intramural Research.....	15.7%
Other Research.....	5.6%	Research Management & Support.....	4.5%
National Research Service Awards.....	2.0%	Cancer Control.....	11.0%
		Construction.....	0.1%

Request totals \$2,060,392,000; Funds for NCI AIDS research are requested through the NIH Office of AIDS Research

Figure 3

Infrastructure of Discovery: Mechanisms and Requested Funding

Supporting the achievement of the goals and objectives of the NCI is an infrastructure of researchers, research institutions, training, applications research, and cancer surveillance. In this section we briefly outline the components of this infrastructure of discovery and the funding necessary to continue making advances against cancer.

Research Project Grants: The "gold standard" of scientific accomplishment is the creation of new knowledge through research. The Nation's researchers represent the single most valuable resource of the research program. To foster the creativity of this vital national resource and provide the freedom to pursue the best ideas that will yield progress against cancer, NCI offers researchers throughout the country the opportunity to compete for research project grants.

The main pool of funds expended by the NCI on extramural research is known as the Research Project Grant (RPG) pool. These dollars represent those funds competitively awarded through peer-review to support dedicated individual cancer investigators in hundreds of academic, medical, public, and private research institutions located in almost every state across the country. Through more than a dozen different types of individual awards (averaging 4 years in duration), the National Cancer Institute in FY 1997 anticipates expending more than \$1,008,451,000 in support of over 3,400 separate research projects. 888 of these awards will be new and competing projects.

Collectively, these research project awards span the full range of basic, clinical, and population-based studies of cancer etiology, biology, prevention, detection, diagnosis, treatment, and control. These grant awards and the dedicated researchers behind them constitute the largest single categorical expenditure of resources that NCI and the extramural research community commits annually to combat cancer. The scientific and medical advances that come from these investments represent the irreplaceable intellectual capital upon which rests the future of cancer research in this country and the world.

Research Project Grants: (in thousands)

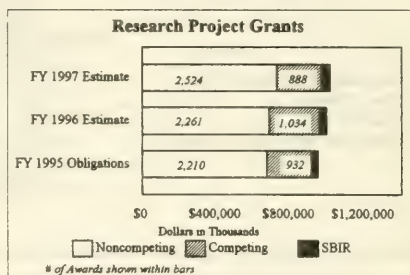
FY1996 Continuing Resolution -- \$991,016

-FY1997 President's Budget -- \$1,008,451

SBIR/STTR included in above:

FY 1996 Continuing Resolution -- \$32,889

FY1997 President's Budget -- \$40,935



The Single Research Project Grant and its Derivatives: This support system has produced many of the most significant research advances in the NCI portfolio. For example, the discovery of BRCA1, the first confirmed hereditary gene for breast cancer, was recently announced by an NCI supported grantee. The discovery of oncogenes that lead to cancer and their relationship to cellular genes, which earned the Nobel Prize for Physiology or Medicine, was made and continues to advance under NCI awards.

The discovery of new tumor suppressor genes ("anti-oncogenes") and their mechanism of action is an area now being explored with substantial NCI grant support. Most recently, NCI grantees have opened new vistas of understanding about how cells that sustain DNA damage that might lead to uncontrolled division can instead be directed either to complete successful repair, or to self-destruct and die through a process called apoptosis. These findings, in turn, have provided new insights into mechanisms of drug action and possible new therapeutic targets.

The single project award will continue to lead to new fundamental discoveries about cancer.

The Program Project Mechanism: The Program Project Grant is an investigator-initiated multi-component award through which groups of researchers pursuing thematically related research projects that require additional shared resources such as specialized core research facilities can be peer-reviewed and supported under a single award. This approach is especially useful in promoting interdisciplinary and translational research where basic and clinical projects are combined and where "critical mass" effects lead to synergy between the investigators.

This type of approach is exemplified by a very large program project centered in Seattle that has led the way in developing of both basic bone marrow transplant biology and its clinical application in high dose chemotherapy regimens for several different types of cancers. The Nobel Prize for Physiology or Medicine was awarded in conjunction with some of the work performed under this award. Another program project in Boston has played a key role in expanding our understanding of the relationship between blood vessel formation and solid tumors. This research has materially advanced knowledge about how vascularization is needed to sustain tumors, and how this knowledge can be used to fight tumor development.

The program project mechanism gives investigators access to a much broader range of projects and common access to patients and tissue samples that would be difficult if not impossible to arrange in a single project setting.

Intramural research: The NCI Intramural Research Program includes the Divisions of Basic Sciences, Clinical Sciences, and Epidemiology and Genetics and is one model of a comprehensive effort to understand and diminish cancer. With the FY1997 budget for cancer of approximately \$325 million, scientists, technical, and support staff, as well as research fellows and visiting scientists from around the world conduct basic, clinical, and population based research in all the cancer research areas. These include cancer biology, causes and predisposition, and clinical investigation in the areas of prevention, detection, diagnosis and treatment. NCI intramural

epidemiologists have rapidly provided information in response to public concerns about alleged possible causes of cancer such as portable telephones and fluoride in drinking water.

A large number of NCI intramural researchers are recognized leaders in their fields as reflected by citations of their work by other scientists, service on editorial boards of peer-reviewed scientific journals, and the prizes and honors they receive. Many NCI intramural scientists collaborate with investigators across the Nation and around the world and with the biotechnology and pharmaceutical industries to accelerate the application of new knowledge to development of products to benefit human health. In fiscal year 1996, significant steps have been taken to ensure careful stewardship of resources and uniform standards of excellence in a stimulating environment where young people receive mentorship, training, and inspiration and where scientists at all stages of their careers are encouraged and stimulated to be creative and strive for critically important knowledge. These initiatives are described in a new widely distributed manual, *National Cancer Institute: Intramural Organization and Principles*.

The IRP has long served as a training locus for cancer researchers in all fields, and many of the leading scientists across the country and in other nations have been trained in its clinics and laboratories. It continues to serve as an important resource to train the next generation of men and women who will carry forward the quest for knowledge that will lead us to successful strategies to prevent and cure cancer that we so deeply desire.

The intramural clinical research program is housed principally in the NIH Warren G. Magnuson Clinical Center where patients from across the country are treated only on research protocols. The Clinical Center is a unique resource for investigators to develop and test novel therapies derived from our growing body of knowledge. It provides a pivotal setting for the NIH community that facilitates the rapid transfer of new information from the laboratory to the patient and back to the laboratory in the search to understand the nature of cancer and how to tame it.

The existence of the IRP is central to the identity of the National Cancer Institute as a scientific, not a bureaucratic, organization. Many physicians who manage NCI extramural grants and programs spend part of each week doing research in the Clinical Center and would not stay in key administrative and managerial jobs without this opportunity. Interchange between active researchers, the scientists who manage the grant portfolios, and the scientist executives who direct the institute and set priorities and directions enriches the quality of decision making and continually reminds all of us of our mission: to learn how to reduce death and suffering from cancer.

The Kidney Cancer (Von-Hippel Lindau) Tumor Suppressor Gene

Cancer results from the accumulation of alterations in the expression of a small number of critical genes. Recently, defects in one particular gene have been shown to be responsible for a rare inherited form of cancer in families with Von

Hippel-Lindau (VHL) disease. This inherited cancer syndrome is characterized by the development of multiple tumors, including kidney cancer, kidney cysts and non-malignant tumors in the adrenal glands. Abnormalities of the VHL gene have also been identified in tumor tissue from the majority of the 25,000 patients diagnosed each year in the United States with sporadic (not inherited) kidney cancer. NIH intramural investigators recently made a key discovery about the role of a protein associated with VHL disease. They determined that the protein produced by the VHL gene plays a role in regulating "transcription elongation," a new mechanism of action for a tumor suppressor gene. Recent experiments have shown that the VHL protein may also be able to sense whether cells are communicating with each other, suggesting that the VHL gene product is important to maintaining the normal tissue architecture that is always lost in the transformation of a normal cell to a cancer cell. These findings open new approaches to studies of cell growth regulation in normal and malignant cells, and could lead to new ways to prevent and treat cancer.

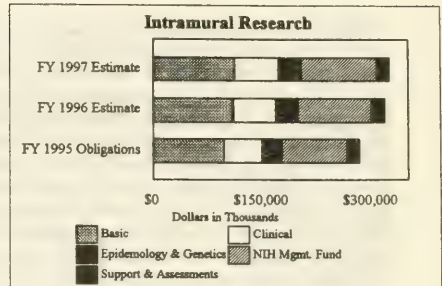
Immunotherapy of Metastatic Carcinomas

Over the last decade, advances in cancer research such as development of new screening, detection and diagnosis technologies, and treatment strategies are increasing survival and improving the quality of life for cancer patients. However, cancer remains a formidable problem, and new approaches are needed to reduce the burden of this disease. One new approach to cancer treatment is immunotherapy. A strategy being used by NCI-supported researchers is to attach very toxic protein molecules capable of killing tumor cells to antibodies that are specific for the tumor cells. A group of NCI intramural investigators have isolated an antibody that reacts with many of the most common malignancies such as colon, lung and breast cancers, and attached a genetically modified form of a powerful bacterial toxin (*Pseudomonas* exotoxin A) to it to make a drug which specifically kills these types of cancers. These new drugs are called immunotoxins. Clinical trials of immunotoxin LMB-1 have resulted in disease regression in five patients with tumors: three with colon cancer and two with breast cancer. The most dramatic response was observed in a man with metastatic colon cancer, who had a large tumor mass in his abdominal cavity which caused pain and diarrhea, and also had tumor cells in the lymph nodes in his neck. Following two courses of LMB-1, the tumor decreased in size by more than 75%, the pain and diarrhea completely disappeared, and the patient returned to work. These studies show that immunotoxins directed at colon, breast, and other epithelial malignancies may be useful in the treatment of human cancers.

Intramural research: (in thousands)

FY1996 Continuing Resolution — \$316,420

FY1997 President's Budget — \$323,754



Cancer Centers: NCI-supported cancer centers currently represent 55 of the strongest academic and free-standing institutions in the nation dedicated to scientific innovation and excellence; to interdisciplinary research, training and education; and to coordinated recognition and pursuit of new research opportunities. Cancer centers are committed to transferring new knowledge to practical clinical and community applications that will reduce cancer incidence, morbidity, and mortality and increase the survival and quality of life of cancer patients. These institutions have the dynamic, flexible research infrastructures and organizational capabilities that consistently promote and sustain the kinds of collaboration between basic, clinical, and population scientists needed to address the complicated questions associated with cancer causation and progression.

Research activities on the molecular and cellular dynamics of cancer cells, vaccine development, novel approaches to gene therapy, and prevention and control interventions all illustrate the need for such effective collaborative enterprises. Cancer centers achieve their objectives by providing a framework that stimulates the participation of a broad range of diverse, but complementary scientific interests. They provide ready access to the most advanced research technologies and services, assure a close association between state-of-the-art research and state-of-the-art care activities within the institution, develop key collaborations with industrial, community, and state health organizations, and link the research capabilities and expertise of scientists within the institution to problems of cancer incidence and mortality in their communities and regions. With their broad geographic distribution, cancer centers are key partners and, in many ways, a principal vanguard of the National Cancer Institute in bringing the benefits of research more directly to local communities and regions of the country.

A critical role of NCI cancer centers is to effectively move laboratory discoveries into patient and population research settings (i.e., translational research), fully exploring opportunities that are likely to have a more immediate impact on the prevention and cure of human cancers. The many successes of centers are

exemplified by their competitiveness in obtaining support through Specialized Programs of Research Excellence (SPoREs), which focus exclusively on translational research. For example:

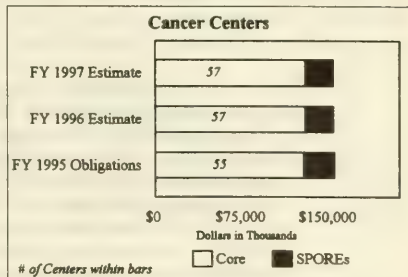
The Breast Cancer SPoRE in the Lineberger Comprehensive Cancer Center at the University of North Carolina is combining molecular, epidemiologic and public health research approaches designed to reduce breast cancer incidence and mortality in rural black populations. This is a clear demonstration of how research excellence organized across a broad spectrum of scientific disciplines is directly benefiting a community and region, one of the prime responsibilities of NCI-designated Comprehensive Cancer Centers.

The University of Michigan Comprehensive Cancer Center recently received a Prostate Cancer SPoRE award. This is an excellent example of the ability of a cancer center to harness institutional resources, to assemble a multi-disciplinary team of basic, clinical, and physical scientists dedicated to understanding a major form of human cancer. This new group was recruited over a two-year period and is working to improve the use of prostate specific antigen (PSA) in combination with cytogenetics as a prognostic marker, and to explore novel Doppler imaging technologies to move ultrasound diagnosis from a two-dimensional to a three-dimensional standard.

Cancer Centers: (in thousands)

FY1996 Continuing Resolution — \$152,647

FY1997 President's Budget — \$152,447



Clinical Trials: A strong clinical research structure including a comprehensive program of clinical trials in treatment, early detection, and prevention is a critical component of the NCI research program. The components of the program include the cancer centers described above and the cooperative groups described in the following section. The Community Clinical Oncology Program (CCOP) is also a crucial component, extending the opportunity for participation in clinical trials to communities across the country.

Our ability to conduct clinical trials is in danger of being compromised by changes in the health care system. In the past, institutions have used patient care surpluses to supplement government research support. The advent of managed care has all but eliminated those discretionary funds. As a result, institutions can no longer sponsor research activities requiring capital expenditures and cannot support essential training for young investigators. These changes pose a very real danger for the continuation of cancer research and our ultimate victory against cancer.

***Cooperative Group Clinical Trials Program:** The nationwide cooperative group program promotes and supports clinical trials in cancer early detection, treatment, and rehabilitation. More than 1,400 institutions and 9,000 investigators participate in these cooperative group studies.

TESTICULAR CANCER

Testicular cancer is the most common malignancy in men ages 15 to 35, striking at a time when a young man cannot believe he could be at risk of cancer. The most aggressive form, non-seminomatous testicular cancer, is often diagnosed at an advanced stage. Twenty years ago, it was nearly uniformly fatal if it had spread beyond the testicle. But thanks to clinical research and therapeutic trials, the outlook has completely changed, dramatically altering the view of this once dread disease for patients, their loved ones, and the medical community. The first trial of the highly curative regimen, cisplatin, vinblastine, and bleomycin (PVB), was initiated in 1974; initial results were reported in May 1976, and the full study report was published in 1977.

It was early 1976, and I had just gotten married the previous summer. I started my first job after graduating from college. I kept telling myself that the growth I felt in my right testicle could not be serious. When I could no longer ignore it, I went to the library and read about cancers of the testicle. The latest edition of a medical reference book made the outlook for testicular cancer seem bleak, so I retreated back into my private terror, praying that I did not have cancer. By that summer, when the back started hurting, I couldn't hide it any longer from myself or my wife. We made an appointment with the doctor. The diagnosis of advanced testicular cancer was made. I was referred to a medical oncologist, who told us that a newly developed chemotherapy regimen had been showing dramatic success. Desperate, I took the new treatment, which lasted four months. That was nearly 20 years ago.

This man was in the first national wave of men cured of non-seminomatous testicular cancer as use of the successful PVB regimen spread even before medical reference books could print the advances. Within a year of the first research report, mortality rates from the cancer were falling nationwide. Now, about 80 percent of men with advanced disease are cured, and overall about 90 percent are cured. But success brought new research questions to be addressed in clinical studies.

By 1985, we were finally convinced that Bill was cured; but we wondered if it was possible, or safe, to start a family. When we asked the doctor, she said there were ongoing studies to determine the fertility of cured testicular patients. She asked if we would participate in such a study. We were happy to, considering how much we had benefitted from the clinical studies on patients that had come before Bill. We found out his sperm count was low, but that having children might be possible. The few children born to patients up to that time were reported to be healthy. Our little girl is now in the third grade, and our son just started kindergarten.

Clinical researchers have recently been studying how to maintain high cure rates while decreasing the side effects of treatment and improving quality of life. Through a series of studies, clinical practice has changed. We now know that less toxic drugs can be used to achieve the same cure rates. Some patients can receive fewer courses of chemotherapy. In fact, because therapy is so effective, carefully selected patients can even be observed after surgery alone, reserving chemotherapy for relapse, yet achieving the same cure rates. Nerve-sparing surgery can be used to preserve the nerves that control ejaculation. Finally, we are studying the genetic and molecular markers that may distinguish different types of testicular cancer, such as an abnormality on the short arm of chromosome 12.

This gratifying success since 1975 also had its effect on the medical community. One doctor recalls:

I started my medical internship in the summer of 1973. One of my first patients had advanced non-seminomatous testicular cancer. My attending physician described the dismal prognosis on morning rounds. The patient died within six months. Before I finished my residency in 1976, we were treating and routinely curing such patients with four monthly courses of PVB chemotherapy. I saw with my own eyes the value of clinical research. That's part of the reason I went into research as a career.

The sheer number of different types of cancers and the biological complexity of individual cancers present extraordinary challenges to the efficient clinical investigation of new anti-cancer agents or new treatment strategies suggested by laboratory and animal experiments. To more rapidly test such potential treatment advances in patients, the NCI maintains a standing funded clinical trials program to conduct such investigations. In this way, new clinical trial organizations do not have

to be created each time a potential new cancer treatment emerges. Nine NCI-sponsored Cooperative Groups place approximately 20,000 new patients onto cancer treatment protocols annually, principally large randomized Phase III clinical trials that have been responsible for establishing the current state-of-the-art for cancer treatment worldwide.

In addition, new anti-cancer agents being studied for the first time in patients are entered into Phase I and Phase II clinical trials; many of these early treatment clinical trials are conducted under NCI Investigational New Drug (IND) sponsorship in institutions funded by NCI cooperative agreement grants. Currently, over 200 investigational agents or treatment strategies, ranging from new chemotherapy drugs and cancer vaccines to agents that prevent tumor blood vessel development, are being studied under NCI INDs. Many of these agents are being developed clinically as a result of active NCI cooperation with biotechnology and pharmaceutical companies, accelerating the clinical testing of scientific advances emerging from these sources. Others come from the scientific laboratories and discovery programs of the NCI itself. Examples of important new anti-cancer agents that have recently come from NCI development include paclitaxel (Taxol®) for ovarian and breast cancers, interferon alpha for malignant melanoma and chronic myelocytic leukemia, fludarabine for chronic lymphocytic leukemia, and trans-retinoic acid for acute promyelocytic leukemia.

Science is increasingly delineating the distinct biological bases for many tumors. As a result, many clinical trials of new treatments are linked to particular laboratory studies, and many NCI trials now include laboratory components in addition to the clinical evaluations. For example, clinical studies of new acute leukemia treatments now routinely include the analysis of genetic changes in the malignant leukemia cells of the individual patient. The NCI has funded small clinical trials groups especially to evaluate potential new treatments for patients with brain tumors, malignancies occurring in the setting of AIDS, and pediatric tumors, due to the very specialized nature of these cancers. A similar program has very recently been established to develop new therapies for breast cancer. Furthermore, recognition of gender, age-related, and ethnic differences in individual responses to cancer therapy has led to initiatives to make such evaluations a routine part of the clinical development of new anti-cancer agents. A recent NCI evaluation shows that minority populations participate in treatment clinical trials in proportion to their cancer risk. Minority participation in clinical research is a high priority for the Institute.

The NCI Role in the Development of Paclitaxel (Taxol®): Paclitaxel is a plant-derived drug originally identified through the NCI's natural products screening program and brought into clinical trial by the NCI in the mid 1980s. The drug has been found to have important anti-tumor activity in patients with ovarian and breast cancers. For example, protocol GOG 111 by the Gynecologic Oncology Group, one of the NCI Cooperative Groups, recently demonstrated a 50 percent increase in median survival time among women with advanced ovarian cancer who were treated with the combination of paclitaxel and cisplatin compared with the standard approach of cisplatin with cyclophosphamide. The NCI has collaborated with Bristol-Myers Squibb in the clinical development of paclitaxel under a CRADA (Cooperative Research and Development Agreement).

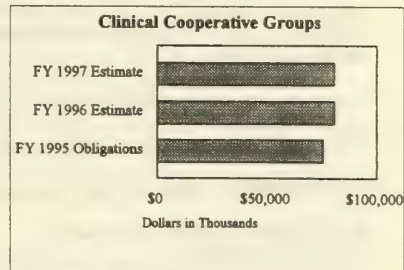
The NCI Role in the Development of All-trans Retinoic Acid ("Vesanoid") for Acute Promyelocytic Leukemia: Acute promyelocytic leukemia (APL) is a form of acute leukemia affecting more than 500 individuals in the United States annually. The disease is treated with aggressive chemotherapy associated with risks of fatal infections and bleeding. Once initial chemotherapy approaches -- sometimes including bone marrow transplantation -- have failed, the disease is frequently fatal. Following research results from China of complete disappearance of malignant cells in patients receiving all-trans retinoic acid, an orally administered modification of Vitamin A, the NCI moved rapidly to make the drug available to patients with APL in whom initial chemotherapy had failed. In collaboration with the pharmaceutical company Hoffman LaRoche, the NCI obtained a clinical supply of all-trans retinoic acid. Over the last three years over 1600 patients with relapsed APL have received the drug, shipped overnight by the NCI after request by the treating hematologist or oncologist. Information gathered from this experience was critical in the FDA evaluation of the agent, and Vesanoid was approved by the FDA for general availability in December of 1995. Meanwhile, an NCI-sponsored randomized clinical trial involving the major adult and pediatric cooperative groups, and evaluating the role of Vesanoid combined with chemotherapy in the initial treatment of APL has been recently completed. The results clearly demonstrate the benefits of combining Vesanoid with available best chemotherapy, and represent a major advance in the treatment of malignancy.

Greater patient access to advanced therapeutic approaches has been a chief goal of the NCI clinical trials program. The field of childhood cancers is a success in this regard. More than 90 percent of children who develop cancer in the United States annually are treated at institutions participating in the NCI-sponsored pediatric Cooperative Groups. While the percentage of adults with tumors treated on protocols is much smaller (on the order of three percent), more than 8,500 oncologists participate in NCI trials, allowing patients to benefit from advanced treatment approaches whether they are seen at the most comprehensive cancer center or the smallest community hospital.

Clinical Cooperative Groups Clinical Trials:
(in thousands)

FY1996 Continuing Resolution -- \$80,594

FY1997 President's Budget -- \$80,394



***Community Clinical Oncology Programs (CCOPs):** The Community Clinical Oncology Program (CCOP) is a mechanism that links community cancer specialists and primary care physicians with clinical Cooperative Groups and cancer centers to conduct cancer treatment, prevention, and control clinical trials. Currently, there are 52 CCOPs in 30 states, with 300 participating hospitals where approximately 3,000 physicians cooperate to enter patients and individuals at risk for cancer on NCI-approved clinical trials. An additional 10 minority-based CCOPs are funded to enhance the participation of minority populations in clinical trials research. These programs are located in nine states and Puerto Rico, bringing an additional 42 hospitals and 350 physicians into the clinical trials network. Through this network, individuals can access state-of-the-art clinical research trials while remaining in their home communities.

Each year the CCOPs enter about 4,000 patients into cancer treatment clinical trials (accounting for about one-third of all patients on NCI treatment efficacy trials). An additional 4,000 participants are entered onto cancer prevention and control clinical trials from the CCOP communities. Support is also provided for university members and affiliates to participate in prevention and control research.

The current CCOP program covers the spectrum from testing new combinations of anti-tumor drugs in cancer patients to providing high risk, but otherwise healthy men and women with agents for the purpose of preventing first occurrences of cancer. Examples of the latter are the Breast Cancer Prevention trial and the Prostate Cancer Prevention Trial. CCOPs have also demonstrated successful interventions for symptom management and continuing care of cancer patients, including treatment for mucositis and hot flashes, common side effects of chemotherapy. The program is rapidly evolving to include interventions for individuals with specific molecular alterations associated with genetic cancer susceptibilities.

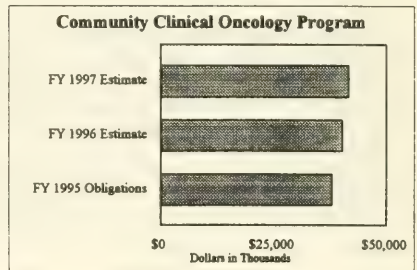
Linking the community, university researchers, and the National Cancer Institute, the CCOPs have proven to be one of the critical paths for the dissemination of state-of-the-art cancer treatment information. The CCOP research network is well positioned to conduct the research of the future that will move oncologic practice from the treatment of established disease to the management of cancer risk.

Community Clinical Oncology Program:
(in thousands)

FY1996 Continuing Resolution — \$38,696

FY1997 President's Budget — \$41,212

(Funds for CCOPs are included within the Cancer Control budget mechanism)



The Breast Cancer Prevention Trial (BCPT) is a randomized clinical trial testing the effectiveness of tamoxifen for preventing breast cancer. Sixteen thousand women at increased risk of developing breast cancer (based on factors such as age, family history, and personal history) are being recruited. Twenty percent of BCPT participants have two or more first-degree relatives (mothers, sisters, daughters) with a history of breast cancer, thus providing a unique resource for understanding breast cancer genetics. The average relative risk for BCPT participants is about five times as great as a comparable group of individuals in the general population. For one group of trial participants, those with lobular carcinoma in situ (LCIS), the risk of developing breast cancer is nearly 16 times the average risk -- equivalent to a near certainty of eventually developing this disease. Studying preventive regimens in these groups may well give us the greatest insight into how cancer prevention can be realized.

The trial is being conducted by the National Adjuvant Breast and Bowel Project (NSABP) in more than 200 sites across the United States, including CCOPs and NSABP members and affiliates. Due to the meticulous collection of data about participants, the BCPT is likely to allow unprecedented opportunities for advancing the scientific understanding of women's health and for studying the effect of tamoxifen in women with predisposing genetic susceptibility to breast cancer. If proven effective, tamoxifen could provide an option to prevent breast cancer in certain women at high risk of developing the disease.

Training and Education: The Cancer Training Program is a critical resource to the National Cancer Institute. It supports a broad range of training activities, individual fellowships and career awards, and education grants in the finest academic and free-standing institutions in the country. Because those trained in research today will form the NCI's intellectual foundation in the basic, clinical, and population sciences ten years from now, training activities sponsored by the NCI must continually anticipate the human resource needs of cancer research in the future. The quality and progress of the Nation's cancer research effort tomorrow will depend directly on the quantity and quality of the individuals who are attracted to careers in cancer research today, and on the appropriateness of the strategies used to train these individuals. Rapid advances in our basic understanding of genetic and molecular changes contributing to the growth and spread of cancer cells provide increasing opportunities to move this knowledge into patient and population research settings and to have a direct, more significant impact on reducing cancer incidence and mortality through new screening, prevention, diagnostic, and therapeutic interventions. Without adequate training, the Nation's scientific and medical workforce will be unable to bring these discoveries to the benefit of the people.

To meet this challenge, the NCI is pursuing four interdependent training and education strategies. The first is to maintain the critical mass of independent basic scientists studying cancer at the most fundamental levels of genetics and molecular biology; basic discoveries will always generate the new knowledge critical for continued progress in eliminating cancer. The second is to encourage

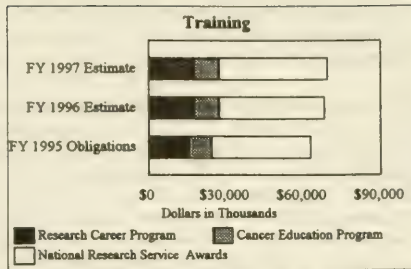
a greater proportion of well-trained basic scientists to shift their interests in model systems to human biology and human disease; it is clear that the complex objectives of cancer research will depend more and more on effective collaborations between basic scientists and clinical and population scientists. The third is to focus on attracting more young physicians and public health specialists into cancer research; of particular importance will be to develop and sustain training programs that will markedly improve the quality and quantity of physicians trained in the clinical sciences, as well as continue programs that will develop a larger contingent of physicians and public health specialists in the biostatistical, epidemiological, behavioral and other prevention and control sciences.

The fourth strategy is to use education grants to improve the curriculum for medical and public health students, and to improve community education and information dissemination programs; a critical issue is how to encourage those in the health care arena and the lay public to maximize the effectiveness of current information and knowledge.

NCI continues to support extensive training and career development programs for minority individuals in order to increase the number of biomedical scientists from under-represented population groups and to increase the number of research personnel leading us into the next century. This investment in intellectual resources is expected to pay off through the expansion of the nation's ability to identify and respond to cancer trends among all sectors of the population. The Comprehensive Minority Biomedical Training Program supports these activities through several mechanisms, including recently developed minority medical oncology awards intended to encourage newly trained clinicians to acquire clinical research experience in oncology. Of particular importance is the emphasis the program places on issues directly related to the health status of minority populations. Other NCI training programs support minority students in the pre- and post-doctoral phase of development, with awards made through the National Research Service Awards, career development awards, supplements to institutional awards, and cancer education grants.

Barriers to the success of the four strategies are significant. Changes in the health care system (i.e. managed care) are threatening the capability of institutions to conduct clinical research and discouraging young physicians from pursuing research careers. We must overcome these barriers. Cancer research training, by strengthening our basic sciences and the collective ability of basic, clinical and population scientists to think and work together, is an essential underpinning of our efforts to improve public health by eradicating the blight of cancer.

This budget request provides a 2.2% stipend increase for the National Research Service Awards.

*Training and Education: (in thousands)**FY1996 Continuing Resolution -- \$68,157**FY1997 President's Budget -- \$69,157*

Research & Development Contracts: Research is a complex enterprise that only flourishes in the context of a strong, reliable support infrastructure. Contracts are a primary mechanism that the Institute uses to provide support for research, information dissemination and management. Generally awarded on a competitive basis for 3 to 5 years depending on the project, contracts are either completed or the project is recompetes at the end of the contract period.

Contracts support a variety of research activities, such as components of drug development, cancer control, epidemiology (including the SEER cancer surveillance program), cancer biology, and information dissemination activities, including the Cancer Information Service. Contracts principally support program development activities in which the NCI defines the area of work, provides guidelines as to how the work will be accomplished, and establishes specific deliverables. The use of contracts is exemplified in the drug development program where a range of services are acquired to support drug screening, synthesis, acquisition, preclinical testing, pharmacology, toxicology, and drug formulation--all sequential activities necessary to produce a new drug. The programs that employ contracts are broad and diverse, with a vital role in supporting laboratory and clinical research, the Institute's management infrastructure, and information dissemination to both the public and the scientific community.

The contract mechanism is extremely useful for research support when the functions to be performed can be identified at the outset of the program or project. When a specific end product is desired or a project needs to be conducted with the NCI's direct involvement, the contract mechanism is appropriate. NCI uses contracts when grant mechanisms are inappropriate, such as for the maintenance of public information services, research databases and drug screening.

A good example of NCI's use of the contract mechanism is the operation of an in vitro cell-based drug screen to discover new agents with potential therapeutic value for cancer and HIV. The drug screen has helped to identify compounds with confirmed anti-cancer and/or anti-HIV activity from either synthetic chemical compounds or natural products. Contracts enable NCI to maintain a vigorous acquisition program for procuring both chemically defined synthetic

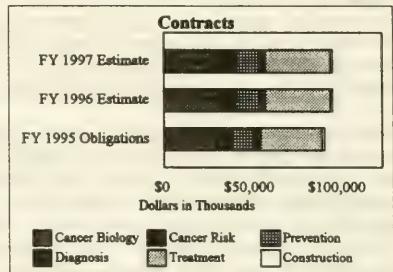
compounds and crude natural products from all over the world for examination in this high-volume screen. More than 100,000 screening assays on approximately 50,000 compounds (half are from natural products) have been performed.

Taxol® is an example of a natural product derivative with striking antitumor activity initially identified by the drug screen. Hydroxyurea, a standard therapy for chronic myelogenous leukemia (CML), was one of the first synthetic chemical compounds with anti-cancer activity identified from early NCI drug screening efforts. Since then, hydroxyurea has also been shown to have therapeutic value for sickle cell anemia and recently, anti-HIV activity. The ability to rapidly screen and identify compounds with special activity against particular human cell types facilitates the preclinical and clinical development of drugs targeted for specific tumors. The contract mechanism facilitates this process. After pharmacologic and toxicologic studies, promising agents enter clinical trials — intramurally or extramurally.

Research & Development Contracts: (in thousands)

FY1996 Continuing Resolution — \$88,424

FY1997 President's Budget — \$96,153



Cancer Control: This section profiles the resources needed for cancer control, which was described earlier as efforts to ensure full, effective utilization of research results. Consensus among experts on the usefulness of new medical knowledge does not guarantee its widespread application. Cancer control, as supported by NCI, addresses this challenge by examining the requirements for translation of proven technologies and tested methodologies into routine practice in the community. Among the requirements may be the removal of barriers to application often found in areas of information dissemination, access to health care services, or cultural conventions. These barriers may be present in the home, the community, the environment, or at the interface with the health care system.

NCI's cancer control activities include a special focus on population groups who bear excessive risks for cancer or who lack access to state-of-the-art cancer services. Research efforts have been undertaken with the collaboration of community and private sector organizations which can be mobilized to assist these population groups. Research networks of minority investigators and leadership groups of community representatives have been established to help accomplish NCI's cancer control objectives.

Important to the process of technology transfer, NCI's activities in information dissemination include programs for both the public and health professionals. These programs are based upon population needs identified through epidemiologic studies and market research among specific population groups. This allows for the design of programs that are relevant and understandable to each group. Information can be disseminated nationally through NCI's patient education program, the leadership initiatives for special populations, minority research networks and the Cancer Information Service.

Cancer surveillance is a critical component of cancer control and, in fact, underlies the entire NCI research portfolio. The tracking and analysis of trends in cancer incidence, mortality, and survival rates stimulate new activities and monitor the effects of ongoing programs. The cornerstone of this effort is the Surveillance, Epidemiology, and End Results (SEER) Program, which monitors the cancer burden of the Nation and provides the basis for assessment of individual, organizational and societal factors that can mediate cancer rates both directly and indirectly.

Surveillance: NCI's Surveillance Program tracks and evaluates changes in the occurrence and severity of cancer and is a critical evaluation arm for the program as a whole. Surveillance is also a key component of each part of the research triad, especially population-based research.

Information Dissemination Services: The Cancer Information Service (CIS) serves the Nation through nineteen regional offices covering all fifty states to provide up-to-date cancer information on toll-free telephone lines (1-800-4-CANCER), develop resource directories of cancer-related services, and act as a resource for community outreach programs.

NCI also maintains, among other databases, the Physician Data Query (PDQ) system which contains information on cancer treatment, prevention, early detection, and ongoing clinical trials. The PDQ Patient Information File is geared to the specialized information needs of cancer patients. PDQ information is also available by facsimile in English and Spanish, and on the Internet.

TRACKING PROGRESS: THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) PROGRAM

The SEER program is the most authoritative source of information on cancer incidence, survival, and mortality in the United States. SEER is distinguished by its broad scope and rigorous quality standards which have made it the model for cancer registries throughout the world. Established in 1973, it now includes 22 state and regional registries (covering about 14 percent of the total U.S. population) that report data to NCI. More than 1.7 million cancer cases are in the database, and approximately 150,000 new cancers are registered annually. Data are collected on tumor site, morphology, stage at diagnosis, first course of treatment, patient demographics, and follow-up for vital status. To strengthen information about the

cancer burden borne by defined populations including minorities, the underserved, the elderly, and rural residents, the SEER sample was expanded in 1992 to improve representations of U.S. Hispanic, Asian/Pacific Islander, American Indian, and African American populations.

Updated annually and provided as a public service in print and electronic formats, SEER data are used by thousands of people each year. Users include researchers, people planning public health interventions, and legislators and health planners who want to assess progress and make policy and funding decisions. The public is exposed to SEER data virtually every day, though they may not know its source. Researchers use SEER to identify geographic and population differences in cancer patterns and to study possible links between cancer incidence and occupational, environmental, and lifestyle influences. SEER data increasingly are being used to answer questions about cancer causation, prevention, treatment, and control. For example, the database is now used to identify people at high risk for cancer, to study patterns and outcomes of cancer care, and to assess the extent to which state-of-the-art treatments are used across the country. An innovative linking of SEER and Medicare data now permits important research on patterns and sources of cancer care and the costs of cancer among the elderly.

SPREADING THE WORD: NCI'S INFORMATION DISSEMINATION MANDATE

Information dissemination is a central component of NCI's mission and mandate. NCI reaches all segments of our diverse population with needed cancer information and speeds the assimilation of clinical advances in cancer into standard medical practice through vital programs including:

The Cancer Information Service (CIS)

The CIS provides accurate, up-to-date cancer information to patients and their families, the public, and health care professionals in all 50 states through 19 offices located at NCI-funded cancer centers and other health care institutions. By dialing 1-800-4-CANCER, callers are automatically connected, free of charge, to the office serving their region. Information on specific cancer types, state-of-the-art care, clinical trials, and resources such as support groups or screening and smoking cessation programs is provided in English or Spanish by information specialists who respond to more than 500,000 inquiries annually. The CIS regional offices are also NCI's focal point for state and local level cancer education efforts which particularly target underserved, high-risk, and low literacy populations. The CIS offices also catalog local cancer-related services, catalyze community outreach efforts, and provide print materials and technical assistance to help local organizations sponsor cancer education programs, media campaigns, and other community programs.

The International Cancer Information Center

The ICIC, recently designated a government Reinvention Laboratory, provides an array of cancer information for scientists, health professionals, and the public. PDQ is NCI's comprehensive clinical cancer database, available on-line and via CD-ROM. Updated monthly, PDQ contains the most current information on treatment of over 80 types of cancer, clinical

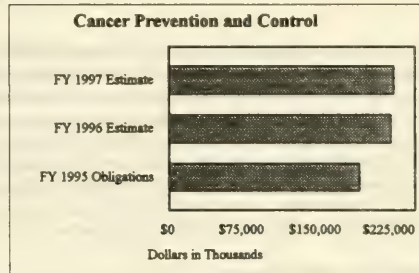
trials open for patient accrual, and cancer prevention, detection, and supportive care updates. PDQ also lists over 21,000 physicians and 8,000 organizations active in cancer care, including FDA-approved screening mammography facilities. The CIS uses these directories daily to provide local referrals to callers.

Portions of PDQ information, NCI Fact Sheets, and other materials are available in Spanish and English 24 hours a day, seven days a week through NCI's CancerFax facsimile system, the Internet, and CancerNet, an e-mail service. CANCERLIT, an abstracted bibliographic database, contains over one million citations describing cancer research results published over the past 30 years. It adds 70,000 citations a year and is updated monthly. NCI also publishes the *Journal of the National Cancer Institute* and peer-reviewed NCI monographs on topics of special interest. All of the ICIC's scientific information services are available through its innovative Information Associates Program, a customer-oriented membership service launched in 1994.

Cancer Control: (in thousands)

FY1996 Continuing Resolution — \$225,000

FY1997 President's Budget — \$227,500



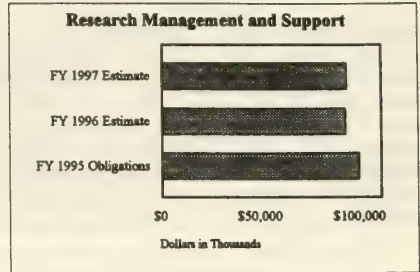
Research Management and Support: Research Management and Support includes activities essential to sustain, guide, and monitor both the extramural and intramural activities of the NCI. These activities include overall scientific program direction and administration by the immediate Office of the Director, with assistance from necessary grant and contract science managers, finance, human resource, legislative, planning and evaluation staff, and the Office of Technology Development. The review and oversight activities of both the National Cancer Advisory Board and the President's Cancer Panel are also included. This segment of the budget also supports NCI's share of central NIH facilities and operations, and extramural staff salaries (intramural salaries are included under the Intramural Research budget). A significant portion of NCI's information dissemination and health education efforts are supported through this part of the budget, including materials prepared for the general public, health and medical professionals, and the scientific and research communities.

Activities supported by Research Management and Support have recently been realigned in accordance with NCI's substantial reorganization and streamlining and reflect a decrease in the FY1996 level consistent with directives to the NIH for administrative reductions.

Research Management and Support:
(in thousands)

FY1996 Continuing Resolution — \$91,629

FY1997 President's Budget — \$92,129

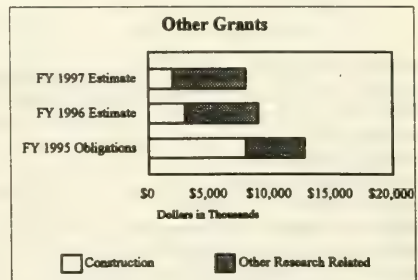


Other Research Support: This area incorporates smaller grant activities such as Conference Grants, Scientific Evaluation, and Construction grants and contracts. Conference awards support meetings, conferences and workshops relevant to promoting the goals of the NCI. Scientific Evaluation awards are the vehicle that supports the scientific review of grant and contract proposals. The grant reviews are conducted by either the NIH Division of Research Grants or the NCI, depending on the granting mechanism. Construction funds provide partial support for the modernization or development of cancer research facilities at institutions located throughout the Nation. Additionally, limited construction funds are provided for repair and improvement at the Frederick Cancer Research and Development Center.

Other Research: (in thousands)

FY96 Continuing Resolution — \$ 8,969

FY97 President's Budget — \$ 7,969



Budget Policy

The FY1997 President's Budget Request of \$2,060,392,000 represents an increase of \$35,098,000 over the FY1996 Continuing Resolution amount. This request maintains the NCI commitment to the entire field of cancer research and will permit the continued expansion of investigator initiated research.

In the FY1997 President's Budget Request, the National Cancer Institute's support for research project grants (RPGs) would increase by 1.8 percent over FY1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 888 competing RPGs and 3,636 total RPGs, an increase of 107 total RPGs over FY1996.

There are several trans-NIH special initiatives for FY1997 in which the NCI will participate significantly. Of the budget increase of \$35,098,000, nearly 50% (or \$17,000,000) is directed to these initiatives as indicated below. The independent investigator initiated grant (Research Project Grant) will be a primary funding vehicle to address new strategies and opportunities in these areas.

New Approaches to Pathogenesis -- \$5,000,000;

New Preventive Strategies Against Disease -- \$4,000,000;

Genetics of Medicine -- \$5,000,000;

Advanced Instrumentation & Computers in Medicine and Research -- \$3,000,000.

Funds for AIDS research conducted by the NCI are included within the NIH Office of AIDS Research (OAR) request.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Research grants						
Research projects:						
Noncompeting.....	2210	\$662,152,000	2261	\$673,142,000	2524	\$715,682,000
Administrative supplementals.....	(257)	11,561,000	(144)	11,500,000	(213)	11,500,000
Competing:						
Renewal.....	359	122,239,000	419	133,078,000	335	116,372,000
New.....	563	113,193,000	611	139,303,000	552	123,902,000
Supplemental.....	10	1,537,000	4	1,104,000	1	60,000
Subtotal, competing.....	932	236,969,000	1034	273,485,000	888	240,334,000
SBIR/STTR.....	191	32,485,000	234	32,889,000	224	40,935,000
Subtotal, research projects.....	3333	943,167,000	3529	991,016,000	3636	1,008,451,000
Research centers:						
Basic research.....	11	20,076,000	11	20,064,000	11	20,064,000
Clinical/comprehensive.....	44	107,681,000	46	109,090,000	46	108,890,000
Subtotal, Core Grants.....	55	127,757,000	57	129,154,000	57	128,954,000
SPORE Grants.....	12	25,535,000	12	23,493,000	12	23,493,000
Subtotal, Centers and SPORES.....	67	153,292,000	69	152,647,000	69	152,447,000
Other research:						
Research career program.....	175	15,686,000	186	17,586,000	186	17,586,000
Cancer education.....	67	8,393,000	66	9,412,000	67	9,412,000
Cooperative clinical research.....	152	74,882,000	152	80,594,000	152	80,394,000
Minority biomedical research support.....	---	2,071,000	---	2,438,000	---	2,438,000
Other research related.....	43	4,690,000	52	5,969,000	52	5,969,000
Subtotal, other research.....	437	105,722,000	456	115,999,000	457	115,799,000
Total, research grants.....	3837	1,202,181,000	4054	1,259,662,000	4162	1,276,697,000

Training:					
Individual awards:					
Noncompeting.....	104	2,880,000	110	3,060,000	112
Competing.....	131	3,446,000	53	1,513,000	55
Subtotal, individual.....	235	6,326,000	163	4,573,000	167
Institutional awards:					
Noncompeting.....	850	22,159,000	850	24,751,000	1057
Competing.....	384	10,086,000	427	11,835,000	216
Subtotal, institutional.....	1234	32,245,000	1277	36,586,000	1273
Total, training.....	1469	38,571,000	1440	41,159,000	1440
Research & development contracts:					
[SBIR contracts].....	120	91,287,000	120	88,424,000	134
	(6)	(1,166,000)	(10)	(1,796,000)	(12)
	FTE		FTE		FTE
Intramural research.....	1246	282,563,000	1230	316,420,000	1230
Research management and support.....	795	98,290,000	770	91,629,000	770
Cancer prevention and control.....	190	192,275,000	187	225,000,000	187
Construction.....		8,000,000		3,000,000	
Total, NCI.....	2231	1,913,167,000	2187	2,025,294,000	2187
Clinical trials.....		(330,597,000)		(336,420,000)	
					(337,237,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Activity

(dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
Research:												
Cancer causation.....	715	\$492,322	620	\$511,158	579	\$525,056	566	\$526,563	566	\$531,623	---	+\$5,060
Detection and diagnosis research.....												
research.....	202	134,339	154	134,199	144	119,951	142	128,874	142	132,143	---	+3,269
Treatment research.....	937	550,568	860	541,502	800	539,656	785	597,328	785	612,740	---	+15,412
Cancer biology.....	459	301,111	475	285,410	440	292,594	431	304,637	431	313,918	---	+9,281
Subtotal, research.....	2313	1,478,340	2109	1,472,269	1963	1,477,257	1924	1,557,402	1924	1,590,424	---	+33,022
Resource Development:												
Cancer centers support.....	18	143,647	13	156,897	13	155,599	13	154,732	13	154,567	---	-165
Research manpower development.....	35	62,899	26	64,086	24	66,723	23	71,751	23	72,741	---	+990
Construction.....	4	7,846	3	16,822	3	8,348	3	3,334	3	2,321	---	-1,013
Subtotal, resource development.....	57	214,392	42	237,805	40	230,670	39	229,817	39	229,629	---	-188
Cancer prevention and control.....	231	112,579	231	153,855	228	204,996	224	238,075	224	240,339	---	+2,264
Subtotal, obligations.....	2601	1,805,311	2382	1,863,929	2231	1,912,923	2187	2,025,294	2187	2,060,392	---	+35,098
Unobligated balance lapsing.....	80			164		244		---		---	---	---
Total, budget authority.....	2601	1,805,391	2382	1,864,093	2231	1,913,167	2187	2,025,294	2187	2,060,392	---	+35,098

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes

1996 Estimated budget authority.....	\$2,025,294,000
1997 Estimated budget authority.....	2,060,392,000
Net Change.....	+35,098,000

Changes:	1996 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
A. Built - in:				
1. Intramural research:				
a. Within grade increase.....		\$114,517,000		+\$1,572,000
b. Annualization of Jan 1996 pay raise.....		114,517,000		+727,000
c. Jan 1997 pay increases.....		114,517,000		+2,626,000
d. Federal employees compensation fund, unem- ployment compensation.....		114,517,000		+19,000
e. Decreased cost of centrally furnished services.....		98,408,000		-861,000
f. Service & supply fund increase.....		17,414,000		+527,000
g. Increased cost of laboratory materials & other expenses.....		86,081,000		+2,033,000
Subtotal.....				+6,643,000
2. Research management & support:				
a. Within grade increase.....		27,372,000		+376,000
b. Annualization of Jan 1996 pay raise.....		27,372,000		+174,000
c. Jan 1997 pay increases.....		27,372,000		+628,000
d. Federal employees compensation fund, unem- ployment compensation.....		27,372,000		+6,000
e. Decreased cost of centrally furnished services.....		13,274,000		-344,000
f. Service & supply fund increase.....		9,098,000		+229,000
g. Increased cost of laboratory materials & other expenses.....		41,885,000		+1,002,000
Subtotal.....				+2,071,000

Summary of Changes--continued

	1996 Current Estimate Base		Change from Base	
	No.	Budget Authority	No.	Budget Authority
3. Cancer prevention & control:				
a. Within grade increase.....		\$13,896,000		+\$191,000
b. Annualization of Jan 1996 pay raise.....		13,896,000		+88,000
c. Jan 1997 pay increases.....		13,896,000		+319,000
d. Decreased cost of centrally furnished services.....		2,024,000		-62,000
e. Service & supply fund increase.....		3,089,000		+34,000
f. Increased cost of laboratory materials & other expenses.....		11,190,000		+280,000
Subtotal.....				+850,000
B. Program:				
1. Research project grants:				
a. Noncompeting.....	2,261	684,642,000	+263	+42,540,000
b. Competing.....	1,034	273,485,000	-146	-33,151,000
c. SBIR/STTR.....	234	32,889,000	-10	+8,046,000
Subtotal.....	3529	991,016,000	+107	+17,435,000
2. Research Centers:				
a. Basic research.....	11	20,064,000	0	0
b. Clinical/comprehensive.....	46	109,090,000	0	-200,000
Subtotal.....	57	129,154,000	0	-200,000
c. SPORE grants.....	12	23,493,000	0	0
Centers & SPORES.....	69	152,647,000	0	-200,000
3. Other research.....	456	115,999,000	+1	-200,000
4. Research training.....	1,440	41,159,000	0	+1,000,000
5. R&D contracts.....	120	88,424,000	+14	+7,729,000
	FTE		FTE	
6. Intramural research.....	1,230	316,420,000	0	+691,000
7. Research management & support.....	770	91,629,000	0	-1,571,000
8. Cancer prevention & control.....	187	225,000,000	0	+1,650,000
9. Construction.....		3,000,000		-1,000,000
Subtotal.....		1,992,405,000		+25,534,000
Total, Changes.....				+35,098,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment.....	2,187	2,187	---
Full-time equivalent of overtime and holiday hours.....	17	17	---
Average ES Salary.....	\$107,942	\$110,101	+\$2,159
Average GM/GS grade.....	10.6	10.6	---
Average GM/GS Salary.....	\$48,236	\$49,683	+\$1,447
Average Salary, grades established by act of July 1, 1944 [42 USC 207].....	\$78,879	\$81,246	+\$2,366
Average salary ungraded positions.....	\$53,318	\$54,491	+\$1,173
Personnel compensation:			
Full-time permanent.....	\$79,602,000	\$81,104,000	+\$1,502,000
Other than full-time permanent.....	17,512,000	18,420,000	+908,000
Other personnel compensation.....	4,842,000	4,986,000	+144,000
Special personal services payments.....	25,228,000	27,611,000	+2,383,000
Total personnel compensation.....	127,184,000	132,121,000	+4,937,000
Personnel benefits.....	28,164,000	29,103,000	+939,000
Benefits to former personnel.....	437,000	454,000	+17,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Travel and transportation			
of persons.....	4,032,000	4,296,000	+264,000
Transportation of things.....	800,000	836,000	+36,000
Rental payments to GSA.....	67,000	71,000	+4,000
Rental payments to others.....	559,000	585,000	+26,000
Communications, utilities, and miscellaneous charges.....	9,650,000	9,787,000	+137,000
Printing and reproduction.....	4,104,000	4,421,000	+317,000
Other services:			
Consulting Services.....	6,408,000	6,821,000	+413,000
Other services.....	42,982,000	48,861,000	+5,879,000
Purchases from Govt. Accts.....	180,172,000	179,595,000	-577,000
Operation of GOCOs.....	34,523,000	33,954,000	-569,000
R&D Contracts.....	162,001,000	156,297,000	-5,704,000
Medical Care.....	203,000	205,000	+2,000
Operation and Maintenance of Equipment.....	6,719,000	6,806,000	+87,000
Supplies and materials.....	24,479,000	24,999,000	+520,000
Equipment.....	11,487,000	11,794,000	+307,000
Grants, subsidies, and contributions.....	1,380,675,000	1,408,737,000	+28,062,000
Insurance claims and indemnities.....	630,000	630,000	—
Interest and dividends.....	18,000	19,000	+1,000
Total authority by object.....	2,025,294,000	2,060,392,000	+35,098,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Administrative Costs

	1995 Actual	1996 Estimate	1997 Estimate	Increase or Decrease
Personnel compensation:				
Full-time permanent (11.1).....	\$78,655,000	\$79,602,000	\$81,104,000	+\$1,502,000
Other than full-time				
permanent (11.3).....	16,201,000	17,512,000	18,420,000	+908,000
Other personnel compensation (11.5).....	4,453,000	4,842,000	4,986,000	+144,000
Special personal				
services payments (11.8).....	21,824,000	25,228,000	27,611,000	+2,383,000
Total personnel compensation (11.9).....	121,133,000	127,184,000	132,121,000	+4,937,000
Personnel benefits (12.0).....	26,183,000	28,164,000	29,103,000	+939,000
Benefits to former personnel (13.0).....	420,000	437,000	454,000	+17,000
Travel and transportation				
of persons (21.0).....	3,803,000	4,032,000	4,296,000	+264,000
Transportation of things (22.0).....	756,000	800,000	836,000	+36,000
Rental payments to others (23.2).....	535,000	559,000	585,000	+26,000
Communications, utilities,				
and miscellaneous charges (23.3).....	9,128,000	9,650,000	9,787,000	+137,000
Printing and reproduction (24.0).....	4,255,000	4,104,000	4,421,000	+317,000
Consulting Services (25.1).....	5,785,000	6,408,000	6,821,000	+413,000
Other services (25.2).....	38,032,000	42,982,000	48,861,000	+5,879,000
Purchases from Govt. Accts (25.3).....	129,820,000	142,029,000	142,277,000	+248,000
Operation of GOCOs (25.4).....	15,636,000	12,269,000	12,269,000	---
Operation and Maintenance of				
Equipment (25.7).....	6,625,000	6,719,000	6,806,000	+87,000
Supplies and materials (26.0).....	22,373,000	23,628,000	24,128,000	+500,000
Total administrative costs.....	384,484,000	408,965,000	422,765,000	+13,800,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

SIGNIFICANT ITEMS IN HOUSE and SENATE
APPROPRIATION COMMITTEE REPORTS1996 House Appropriation Committee Report LanguageItem

Breast Cancer - ... The House in its report 104-209, page 60 states that the Committee recognizes that breast cancer research continues to require a significant allocation of NCI resources in order to decipher the complex mysteries of this disease. The Committee agrees with NCI which places breast cancer research as a high priority within the Institute. Therefore, the Committee directs NCI to continue to strengthen its commitment to breast cancer research, including the National Action Plan on Breast Cancer.

Action Taken or to be Taken

Breast cancer research remains a high priority of the National Cancer Institute's research program. In 1994, a breast cancer susceptibility gene (BRCA-1) responsible for familial early-onset breast and ovarian cancer was mapped to chromosome 17q12-21 and subsequently cloned. More recently, NCI investigators in collaboration with scientists from the National Center for Human Genome Research and the extramural community, discovered a specific BRCA-1 gene mutation in nearly one percent of blood samples collected from women of Ashkenazi (Eastern European) Jewish descent. This finding provides the first evidence that an alteration in the BRCA-1 gene may be present in measurable levels of a specific subgroup in the general population. The NCI is launching a study in the Washington metropolitan area to determine the prevalence of the BRCA-1 mutation in the Ashkenazi Jewish population and to gather relevant medical and family history information.

A recent NCI study involving a follow-up sample of U.S. women found that just under half of breast cancer incidence could be explained on the basis of well-known breast cancer risk factors (e.g., age at first birth and family history of breast cancer). Another NCI study of U.S. regional differences in breast cancer mortality showed that most of the variation could be attributed to differences in the prevalence of recognized breast cancer risk factors.

NCI-supported extramural investigators have analyzed data from 14 years of follow-up of the Nurses' Health Study cohort and found no association between silicone breast implants and connective-tissue diseases. An ongoing NCI study is further evaluating these implants in relation to breast cancer risk. Other NCI and extramural studies are investigating the role of estrogens (endogenous and exogenous), dietary factors (including alcohol intake), and a variety of host factors and environmental exposures in breast cancer risk.

The Long Island Breast Cancer Study Project (LIBCSP) is investigating risk associated with exposures to pesticides, drinking water, air pollution, electromagnetic fields, and hazardous waste, as well as occupational exposures, diet, and various host factors. This collaborative research project is being carried out by consortium of NCI-designated cancer centers and New York hospitals, in addition to NCI-supported grantees.

Ataxia-telangiectasia (A-T) is a rare genetic syndrome characterized by radiosensitivity and predisposition to breast and other forms of cancer. NCI has initiated a number of collaborative projects to investigate this risk among heterozygotes, including an effort to add countries with population-based tumor registries to an ongoing collaborative study of A-T patients and their relatives in Denmark. In another project, blood and tumor tissues are being collected and examined for A-T carrier status in over 1,000 breast cancer cases (including over 50 patients with early-onset disease) that have been identified in studies of radiation-exposed cohorts. A recent NCI workshop on A-T discussed a number of important epidemiologic opportunities to evaluate further the risk of cancer among A-T heterozygotes.

Currently, there is no curative treatment for the most common malignancies such as colon lung and breast, once they have metastasized. NCI researchers have isolated an antibody which reacts with many of these malignancies and attaches the antibody to a genetically modified form of a powerful bacterial toxin to make a drug which specifically kills these types of cancers. These new drugs are called immunotoxins. For the past two years, a clinical trial with immunotoxin LMB-1 has been carried out at the National Cancer Institute. During the initial stages of the trial, five tumor regressions have been observed: three in colon cancer and two in breast.

The Breast Cancer Prevention Trial (BCPT) with tamoxifen is underway in the Community Clinical Oncology Program (CCOP) clinical trials network. This trial is testing the ability of tamoxifen, an anti-estrogen medication of proven efficacy in postsurgical treatment of early stage breast cancer, to prevent the development of breast cancer in women at increased risk for developing the disease.

The NCI has developed a Breast Cancer Education Program Strategic Communications Plan for 1995-1998. The plan focuses on reaching special populations of women ages 50 and over through targeted NCI materials, and includes efforts for developing resources for community-based organizations to assist them in planning their breast cancer and mammography education and outreach programs.

Item

Prostate Cancer - ...The House in its report 104-209, page 60 states that the Committee notes that the incidence of prostate cancer continues to rise, and urges that further effort be placed on research related to early detection, diagnosis, and treatment, particularly among minority Americans.

Action Taken or to be Taken

The NCI continues to place a strong emphasis on research related to detection, diagnosis, and treatment of prostate cancer. An NCI investigation of dietary patterns has found a positive association between prostate cancer risk and increased consumption of dietary fat, particularly saturated fats. In another study, heavy alcohol use was shown to be related to risk in both white and African-American men. Protective factors were suggested from a cohort study that observed reduced prostate cancer risk associated with increasing consumption of lycopene-containing foods, such as tomatoes. An NCI study of genetic and environmental factors related to the development of prostate cancer is underway in large population-based screening trials. Another effort involves a case-control of prostate cancer in Shanghai, which is attempting to identify factors related to the low risk of this malignancy among Chinese men.

In collaboration with NIEHS and National Institute of Diabetes and Digestive and Kidney Diseases, NCI issued a request for grant applications to stimulate new research on molecular epidemiology of prostate cancer. Molecular markers are needed to identify patients at low risk of progression who might be spared aggressive therapy. The identification, and validation of clinically useful molecular markers for prostate cancer remains a high priority of the NCI.

NCI has perfected a new microdissection technology, and used it to make a fundamental genetic discovery about the progression of prostate cancer. This discovery had tremendous implications for the science of prostate cancer, and is leading directly to new screening and prevention measures which could potentially reduce suffering and death caused by prostate cancer.

Researchers from NCI have shown that the estrogen response modifier, Tamoxifen, already in wide use in hormonal therapy of breast carcinomas in women, is a potent suppressor of androgen-promoted carcinogenesis in the prostate complex. Interestingly, although there are no reports of use of Tamoxifen for prostate cancer, in rats the promoting activity of testosterone for prostate carcinogenesis is potentiated by estradiol. These studies suggest that use of Tamoxifen early in the process of carcinogenesis may increase the latency or slow the progression of prostate cancer.

The Prostate Cancer Prevention Trial (PCPT) is being conducted in the Community Clinical Oncology Program (CCOP) clinical trials network. The trial is an intergroup study involving over 225 community and university hospitals across the country. The study tests the ability of finasteride (Proscar), a 5-alpha-reductase inhibitor of androgen synthesis, to reduce the incidence of prostate cancer. Participation is open to all men between ages 55 and 70. Black men and men with family history of prostate cancer are being aggressively recruited because they may have the greatest risk of developing prostate cancer.

Item

Minority populations - ...The House in its report 104-209, page 60 states that the Committee encourages continued research emphasis in breast and prostate cancer and other high priority cancer areas in a concentrated effort to address the needs of minority populations.

Action Taken or to be Taken

NCI's Comprehensive Minority Biomedical Program (CMBP), assisted by the Office of Cancer Communication (OCC), supported contracts to two academic institutions to explore approaches to building cancer prevention awareness in the African American community through historically Black colleges and universities. The purpose of this study is to examine Black Colleges as effective information and education conduits to the Black community. The Historically Black Colleges and Universities (HBCU's) are being utilized as major resources from which effective cancer information and diffusion models can emanate.

The Minority-Based Community Clinical Oncology Program (MBCCOP) provides minority cancer patients with access to state-of-the-art cancer treatment, prevention and control technology. The MBCCOP includes ten programs. Each program has greater than fifty percent of new cancer patients from minority populations. The MBCCOP provides a vehicle to develop and implement effective treatment, prevention and cancer control strategies in minority populations and allows for the study of minority recruitment and accrual to cancer clinical trials.

The NCI supports two initiatives that seek to address the cancer prevention and control needs of minority populations: the National Black Leadership initiative on Cancer, and the Hispanic Leadership Initiative on Cancer. In addition, the NCI is encouraging developmental research in Native Pacific populations to assess their cancer prevention, early detection and treatment needs.

Cancer prevention and control research will receive continued emphasis, attention and encouragement within the Cancer Centers Program. This area of research is well suited to concentrate on cancer problems of special populations such as minorities and Native Americans.

New initiatives will be established to increase information flow on cancer prevention and control to hard-to-reach medically underserved populations. This purpose will be achieved by forming partnerships between minority institutions with affiliated medical schools, NCI funded cancer centers and the communications industry. These partnerships will then be used to develop culturally sensitive programs for transmission on a regular basis and by minority medical staff to the targeted populations.

Item

Leukemia - ...The House in its report 104-209, page 60 states that the Committee recognizes the importance of continued research and clinical trials for leukemia. Noting that changes in health care financing have slowed the development of more effective treatment for leukemia, the Committee urges the NCI to support further leukemia-related translational research for innovative, peer-reviewed clinical trials.

Action Taken or to be Taken

The National Cancer Institute continues its commitment to leukemia and leukemia-related research. Most recently, NCI researchers have demonstrated that Juvenile Chronic Myelogenous Leukemia (JCML) is a clonal disease. This is a landmark finding because clonality defines JCML as a malignancy and provides the basis for future molecular studies to define mutations which cause this rare type of leukemia. Research observations have provided a better understanding of the disease and a strong scientific rationale to devise novel approaches to therapy. On the basis of these findings, a clinical trial using 13-cis retinoic acid in the treatment of JCML has been initiated within one of the NCI's Clinical Cooperative Groups.

Item

Neurofibromatosis - ...The House in its report 104-209, pages 60 and 61 states that the Committee remains fully committed to continuation of an aggressive program of research on neurofibromatosis throughout NIH and urges NIH to ensure that funding levels reflect that priority. This work has already produced major breakthroughs, particularly in areas of genetics and the links between neurofibromatosis, various cancers, and other devastating diseases. The Committee encourages the Institutes at NIH with NF projects to work together with extramural research community to develop a coordinated plan to move this research forward. The Committee encourages NIH in managing this effort to support a variety of collaborative approaches including the possibility of jointly sponsored requests for application and an NIH- wide consensus conference to bring together experts from throughout the world to make recommendations on research opportunities and priorities.

Action Taken or to be Taken

NCI's multi-disciplinary collaborations throughout the NIH and the extramural community have led to expanded knowledge about the genetics of neurofibromatosis 2 (NF2) and the medical complications of this disorder. A major collaboration led to the cloning of the gene. Efforts are continuing to identify mutations in the NF2 gene and to describe the associated clinical characteristics.

Item

Nutrition - ...The House in its report 104-209, page 61 states that the Committee encourages the National Cancer Institute to continue its strong work in the nutrition field and to consider placing a priority within that field on breast cancer research and other research involved with women's health. Chemoprevention, an important activity of this Institute, often relates to substances in the diet. Support of clinical nutrition research units assures that basic information on Chemoprevention is studied in the clinical arena.

Action Taken or to be Taken

The overall goal of NCI's nutrition research portfolio is to provide definitive data for developing quantitative dietary guidance and acceptable food choices that have the potential to substantially reduce the risk of cancer in the general population. NCI's Interactive Research Project Grants support interdisciplinary collaborative research to address the complex questions about quantifying the role of diet and dietary components in cancer prevention. A number of ongoing breast cancer studies, such as the Long Island Breast Cancer Study Project, include the assessment of dietary factors in breast cancer risk, while other studies examine ethnic diversity in diet as it may relate to increased cancer risk. Other studies are examining the impact of modifying dietary fat intake, in addition to the links between cancer and the intake of micronutrients, fruits and vegetables, red meat, and alcohol.

The National 5-A-DAY Program, designed to encourage Americans to eat five or more servings of fruits and vegetables every day, represents a significant public/private partnership between NCI and the Produce for Better Health Foundation. NCI's role as the educator in providing credible information plays an integral part in communicating the 5-A-DAY message. Research grants awarded to state health agencies, universities, and cancer centers are evaluating the effect of 5-A-DAY activities in schools, workplaces and other community settings. Currently, 52 out of 55 (93 percent) state and territorial health agencies are licensed with NCI to conduct 5-A-DAY awareness and behavior changes activities.

In 1995, the NCI developed a Nutrition Education Program Plan that focuses on reaching special populations through targeted NCI materials, the CIS Outreach Program, partnerships, and the media. Additionally, the NCI produced the Action Guide for Healthy Eating brochure that is designed to motivate readers to act by asking them to select action steps they are willing to take to lower fat and increase intake of fiber, fruits, and vegetables.

Item

Translational research - ...The House in its report 104-209, page 61 states that the Committee notes the importance of translational research in moving research advances from the "bench to the bedside". The Committee encourages NCI to address to the extent it can some of the barriers to conducting translational research that were identified in the National Cancer Advisory Board's 1994 report.

Action Taken or to be Taken

Translational research at the NCI is fostered through a number of critical research mechanisms: the NCI Cancer Centers program, NCI-supported Clinical Cooperative Groups, and the Community Clinical Oncology Program (CCOPs). The Cancer Centers are committed to transferring new knowledge to practical clinical and community applications, and the infrastructure and organization of the centers promotes collaborations between basic, clinical, and population scientists. These collaborative efforts are crucial to research activities on molecular and cellular dynamics of cancer cells, vaccine development, novel approaches to gene therapy, and prevention and control interventions. Cancer Centers are able to develop key collaborations with industry and with community and state health organizations to address problems of cancer incidence and mortality in their region.

Increased patient access to advanced therapeutic approaches has been a chief goal of the NCI clinical trials program, but our ability to conduct clinical trials is in danger of being compromised by changes in the health care system. The advent of managed care has all but eliminated the patient care surpluses that institutions used in the past to supplement government research support. Institutions are no longer able to sponsor research activities requiring capital expenditures, and cannot support essential training for young investigators. One way that the NCI addresses this challenge is through its support of the Clinical Cooperative Groups. The Clinical Cooperative Groups extend the opportunity for participation in clinical trials to cancer patients across the country. The efficient clinical investigation of new anti-cancer agents or new treatment strategies suggested by laboratory and animal experiments is complicated by the sheer number of different types of cancers, and the biological complexity of individual cancers. NCI maintains a standing funded clinical trials program in order to more rapidly test such potential treatment advances in patients, eliminating the need for the creation of a new clinical trials organization each time a potential new cancer treatment emerges. The CCOP program is also a crucial component, extending the opportunity for participation in clinical trials to communities across the country.

1996 Senate Report LanguageItem

National Cancer Institute Intramural Review - ...The Senate in its report 104-145, page 69 states that the Committee is very pleased that the NCI Advisory Board ad hoc working group on the Intramural Research Program has conducted an in-depth, thoughtful review of the Intramural Research Program of the NCI. As the largest intramural program within the largest Institute at NIH, it is critical that this research set an example for scientific quality, training of young scientists, intellectual excellence, and effective scientific planning. The Committee looks forward to a report from the new NCI Director at next year's hearing regarding the implementation of the ad hoc groups' recommendation and their impact on NCI's intramural efforts.

Action Taken or to be Taken

The Director will discuss this issue during his testimony before the Committee at the 1997 Appropriations hearings.

Item

Neurofibromatosis - ...The Senate in its report 104-145, page 69 states that the Committee encourages the NCI and other relevant NIH institutes to develop, in consultation with the extramural community, a comprehensive plan for a coordinated research and therapy agenda on NF.

Action Taken or to be Taken

NCI's multi-disciplinary collaborations throughout the NIH and the extramural community have led to expanded knowledge about the genetics of neurofibromatosis 2 (NF2) and the medical complications of this disorder. A major collaboration led to the cloning of the gene. Efforts are continuing to identify mutations in the NF2 gene and to describe the associated clinical characteristics.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Estimate
Research and Investigation.....	Section 301	42 USC241	Indefinite		Indefinite	
National Cancer Institute.....	Title IV, Part A	42 USC285	Indefinite	--> \$1,984,135,000	Indefinite	--> \$2,018,233,000
	(Sec 408 (a)(1)(A))		Indefinite	(1,759,135,000)	Indefinite	(1,790,733,000)
	(Sec 408 (a)(1)(B))		Indefinite	(225,000,000)	Indefinite	(227,500,000)
National Research Service Awards.....	Section 487(d)	42 USC288	Such sums as necessary	41,159,000	Such sums as necessary	42,159,000
Total, Budget Authority.....				2,025,294,000		2,060,392,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Appropriation History

	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1988.....	\$1,302,823,000	\$1,448,411,000	\$1,527,054,000	\$1,469,327,000
1989.....	1,468,256,000	1,593,536,000	1,591,036,000	1,571,879,000
1990.....	1,494,741,000	1,652,666,000	1,668,473,000	1,657,161,000
1990 Sequester				-22,829,000
1991.....	1,694,059,000	1,749,392,000	1,747,462,000	1,714,784,000
1991 Sequester				-22,000
1992.....	1,810,230,000	1,830,509,000	2,010,230,000	1,962,587,000
1993.....	2,010,439,000	1,998,616,000	2,010,439,000	1,981,351,000
1994.....	2,142,122,000	2,082,267,000	2,082,267,000	2,076,382,000
1995.....	1,967,709,000	1,917,929,000	1,917,929,000	1,913,819,000
1996.....	1,994,007,000	2,025,294,000	1,972,757,000	2,025,294,000
1997.....	2,060,392,000			

¹ Reflects enacted supplementals, rescissions and reappropriations.

² Excludes funding for AIDS research. Proposed to be at the Secretary's level.

³ Excludes funds for AIDS research and education [\$125,280,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

⁴ The 1990 request excludes funds for the National HIV program [\$151,332,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

⁵ Excludes enacted administrative reduction of \$6,839,000.

⁶ Excludes \$35,793,000 for NRSA training programs not considered.

⁷ Excludes enacted administrative reductions of \$42,568,000 and \$8,972,000.

⁸ Excludes enacted administrative reductions of \$22,255,000, \$482,000, and \$3,954,000.

⁹ Excludes enacted administrative reductions of \$16,060,000; \$9,933,000; and \$139,000.

¹⁰ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995, FY 1996 and FY 1997.

¹¹ Excludes enacted administrative reductions of \$901,000, \$116,000, and \$1,482,000.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	567	546	546
Division of Basic Sciences.....	619	614	614
Division of Clinical Sciences.....	489	485	485
Division of Cancer Epidemiology and Genetics.....	104	101	101
Division of Cancer Treatment, Diagnosis, and Centers.....	186	175	175
Division of Cancer Biology.....	47	47	47
Division of Cancer Prevention and Control.....	147	147	147
Division of Extramural Activities.....	72	72	72
Total, NCI	2,231	2,187	2,187

Average GS/GM Grade

1992.....	10.3
1993.....	10.3
1994.....	10.7
1995.....	10.5
1996.....	10.6

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Administration

Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
ES-6.....			
ES-5.....	2	2	2
ES-4.....	10	10	10
ES-3.....	1	1	1
ES-2.....	3	3	3
ES-1.....	2	2	2
Subtotal.....	18	18	18
Total-ES Salary.....	\$1,895,200	\$1,942,959	\$1,981,818
GS/GM-15.....	168	142	140
GS/GM-14.....	215	193	186
GS/GM-13.....	197	194	186
GS-12.....	255	266	266
GS-11.....	217	215	215
GS-10.....	7	7	7
GS-9.....	127	126	126
GS-8.....	87	83	83
GS-7.....	234	229	229
GS-6.....	67	64	64
GS-5.....	32	34	34
GS-4.....	66	55	55
GS-3.....	13	12	12
GS-2.....	5	9	9
GS-1.....	4	8	8
Subtotal.....	1,694	1,637	1,620
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General.....	1	1	1
Director Grade.....	1	1	1
Senior Grade.....	64	61	61
Full Grade.....	57	56	56
Senior Assistant Grade.....	60	57	57
Assistant Grade.....	31	30	30
Subtotal.....	214	206	206
Ungraded.....	83	78	76
Total permanent positions.....	1,795	1,733	1,714
Total positions, end of year.....	2,250	2,244	2,244
Total full-time equivalent (FTE), end of year.....	2,231	2,187	2,187
Average ES level.....	3.2	3.2	3.2
Average ES salary.....	\$105,289	\$107,942	\$110,101
Average GS/GM grade.....	10.6	10.6	10.6
Average GS/GM salary.....	\$47,041	\$48,236	\$49,683
Average salary ungraded positions.....	\$51,665	\$53,318	\$54,491

WEDNESDAY, APRIL 24, 1996.

FOGARTY INTERNATIONAL CENTER

WITNESSES

PHILIP E. SCHAMBRA, M.D., DIRECTOR, FOGARTY INTERNATIONAL CENTER

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

STEPHANIE J. BURSENOS, DEPUTY DIRECTOR, FOGARTY INTERNATIONAL CENTER

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. Now we are pleased to welcome Dr. Philip Schambra, the Director of the Fogarty International Center. Dr. Schambra, it's good to see you again. And if you would introduce the woman who's with you and then proceed in any way you want.

INTRODUCTION OF WITNESSES

Dr. SCHAMBRA. Thank you very much, Mr. Porter.

On my left is Ms. Stephanie Burzenos, the Deputy Director of the Fogarty International Center. On my right is Dr. Harold Varmus, the Director of NIH, and Mr. Dennis Williams, the Deputy Assistant Secretary for Budget.

OPENING STATEMENT

Mr. Chairman, if I may, I'd like to submit my complete statement for the record and give a shortened version.

Mr. Chairman, the mission of the Fogarty International Center quite simply is to safeguard the health of the people of the United States through international scientific cooperation. Our highest priority is protecting Americans from health threats that transcend national boundaries.

As we approach a new century, health concerns increasingly have transnational origins and consequences that require international solutions. Unexpected diseases have surfaced due to demographic changes, altered patterns of land use and mutability of disease pathogens. Due to the ease of international travel and trade, disease outbreaks in foreign countries rapidly cross American borders.

In addition, pollutants in the atmosphere, water and food chain are recognized as insidious causes of chronic diseases and dysfunction. Unsustainable population growth in underdeveloped regions of the world also has global consequences for health and quality of life, including worsening pollution and increased risks of infectious diseases.

To illustrate these interrelationships, I'd like to show a chart which depicts the causal relationships between the global trends

and their health consequences. That's the poster on my left. And I hope it vividly illustrates to you what we consider to be our number one priority, that is the Fogarty Center's action against global health threats.

The column to the left under global trends shows the basic circumstances that we have to deal with which lead to the health consequences shown in the middle column, and yields the Fogarty Center's action taken through the programs listed in the last column. Under global trends, of course, we're talking about unsustainable population growth, with its consequences of increased agriculturization and industrialization, urban migration and encroachment upon the natural environment, giving rise to new diseases, reemerging diseases, pollution increase and biodiversity loss.

These Fogarty programs were established in collaboration with other parts of the NIH and other parts of the Government, which I will speak to in the rest of my remarks. These are indeed complex problems that require cooperative interdisciplinary solutions. I should note that these problems were very much on the minds of Congress when the Fogarty Center was established a quarter of a century ago. At that time, the White House and the 90th Congress announced that the primary concerns of the Center would be, "the problem of world population, infectious diseases and environmental determinants of disease."

As the chart illustrates, the Fogarty Center is taking action against these global health threats through specialized training and research grants to American scientists who have relevant programs currently supported by the research components of NIH. A primary goal is to develop teams of highly trained scientists in regions of the world that, due to disease burdens and environmental conditions, provide unique opportunities to understand disease progression and devise methods for prevention and treatment.

Through this investment, the groundwork is laid for international cooperation in field trials of drugs, treatments, vaccines and other new interventions with high promise. Special efforts are made to broaden support and expertise through cooperation with other components of the Public Health Service and the Federal Government.

In fact, Mr. Chairman, you'll be interested to know that nearly 60 percent of the Federal funds managed by FIC are entrusted to the Center by other NIH or other governmental components, who view the Fogarty Center as an important means of advancing their international research and training objectives. These partnerships, many of which are listed on this chart, are an efficient means of reducing costs and streamlining management of international programs.

FIC's AIDS International Training and Research Program, carried out with the support of the Office of AIDS Research, enables NIH-supported investigators to work cooperatively in Africa, Asia and Latin America, to understand the full threat of the AIDS epidemic and develop tools for treatment and intervention. Through studies of populations in regions of the world where the burden of the AIDS virus is greatest, we have increased our understanding of the virulent properties of HIV, risks of transmission and devised

strategies for prevention and therapy. Examples of research advances supported under this program are described in my written statement.

The Fogarty Center's International Research and Training Program in New and Emerging Infectious Diseases, begun just this year, supports cooperative research and training in regions of the world that are the potential origin of new epidemics, employing new molecular and analytic tools in their study. Knowledge gained will support the development of a global research sentinel system capable of detecting and containing future epidemics. This program represents a partnership with the National Institute of Allergy and Infectious Diseases and the Centers for Disease Control and Prevention.

The Fogarty Center's International Training and Research Program in Population and Health supports research to improve reproductive and neonatal health care and demographic capabilities in countries where population growth impedes economic development and quality of life. The goal is to better understand the social and behavioral determinants of population growth, and to develop public health interventions through research. This program was launched in partnership with the National Institute of Child Health and Human Development.

The Fogarty Center's International Training and Research Program in Environmental and Occupational Health positions the United States to work cooperatively with regions of the world with relatively high levels of contaminants in the ambient environment and the work place. With the application of new scientific methods, the effects of environmental agents on human health will be examined and interventions will be devised to reduce health risks. This program is co-funded with the National Institute of Environmental Health Sciences and the CDC's National Institute for Occupational Safety and Health.

The health consequences of environmental degradation also include the potential loss of valuable medicinal products derived from nature. For centuries, plants have been the source of medicines such as digitalis for heart disease and quinine for malaria. The International Cooperative Biodiversity Groups Programs are supported and administered by FIC and designed to discover new drugs from the earth's biological diversity.

In the program's first two years, of more than 2,000 samples collected, 120 have been shown to be biologically active. And these are now being tested as candidate drugs against certain cancers and viral diseases, malaria and degenerative neurological disorders. The program is cost-shared by FIC and several NIH components, the National Science Foundation, the U.S. Agency for International Development and American industries.

Our cost-sharing partnerships extend beyond the United States. In a collaboration with research agencies in the United Kingdom and France, the Fogarty Center is leading efforts working with African scientists to accelerate research on the prevention of malaria in Africa by sharing resources, facilities or field sites, and by developing and exchanging scientific personnel. If successful, this pilot project could be expanded to other high priority public health areas.

The Fogarty Center also has initiated a postdoctoral exchange program for American and Japanese biomedical scientists, funded in its entirety by the Japan Society for the Promotion of Science. American scientists will benefit from new technologies pioneered in Japanese laboratories in such areas as protein engineering and advanced instrumentation.

Mr. Chairman, our namesake, Congressman John Fogarty, your predecessor as Chairman of this Subcommittee, was the beginning of a continuing lineage of Congressmen who have made NIH an international leader not only in the quality of its research but through its humanitarian interactions with more than 100 nations around the globe. In John Fogarty's words, "Our international programs can be characterized as enlightened self interest, since it can be amply demonstrated that we receive as well as give."

As the component of the NIH legislated to improve health through international cooperation, the Fogarty Center is cognizant of its special obligations and its partnership with the American public. Our shared purpose is to ensure that the U.S. scientific community is prepared to meet current and emerging global health threats. The cooperative pursuits of the international community of scientists are key to the future health of the world's citizens and environment, economic prosperity and global security.

Thank you, Mr. Chairman. Our fiscal year 1997 budget request is \$15,790,000. I will be pleased to answer any questions that members of the Subcommittee may have.

[The prepared statement and biography of Dr. Philip Schambra follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
John E. Fogarty International Center
for Advanced Study in the Health Sciences

Mr. Chairman, the Fogarty International Center (FIC) was established by Congress to advance the health of the people of the United States through international scientific cooperation. Of highest priority is the need to protect American citizens from health threats that transcend national borders. In that sense, the Center carries forward an original mandate of the National Institutes of Health (NIH). At the turn of the century, NIH was confronted with diseases imported by immigrant populations, such as cholera and yellow fever. Yet research underway in cooperation with laboratories in Paris, Berlin, London, and other international scientific centers led to antibiotic therapies and immunization. These developments would alter dramatically the practice of clinical medicine, and the health of Americans as well as others around the world.

One hundred years later, we are at a similar watershed. This is due largely to new tools to combat disease made possible through molecular biology and other disciplines. Biomedical research has become a global pursuit to discover genes, proteins, biochemical signals and other properties that may enable scientists to reverse the progression of cancers and inherited disorders at the molecular level, or bolster the immune system against infection. In this era of specialized skills, international cooperation to share ideas and techniques is a requisite for discovery.

Moreover, as we approach a new century, health concerns increasingly have transnational origins and consequences and require international solutions. Unexpected diseases have surfaced due to demographic changes, altered patterns of land use, and the adaptability of disease pathogens. With the ease of international travel and trade, disease outbreaks in foreign countries rapidly cross U.S. borders. Pollutants in the atmosphere, water and food chains are recognized as insidious causes of chronic diseases and dysfunctions. Unsustainable population growth in underdeveloped regions of the world also has global consequences for health and quality of life, including worsening pollution and increased risks of infectious disease.

As the attached chart illustrates, FIC responds to these interrelated challenges through specialized training and research grants to U.S. scientists with programs currently supported by the research institutions at NIH. A primary goal is to develop teams of highly-trained scientists in regions of the world that, due to disease burdens and environmental conditions, provide unique opportunities to understand disease progression and devise methods of prevention and treatment. Through this investment, the groundwork is laid for international cooperation in field trials of drugs, treatments, vaccines, and other new interventions of high promise.

FIC programs are developed as joint ventures with our sister institutes at NIH. Special efforts also are made to broaden support and expertise through cooperation with other components of the Public Health Service and Federal government. In fact, nearly 60 percent of the Federal funds managed by FIC are entrusted to the Center by other NIH or other Federal components who view FIC as an important means of advancing their international research and training objectives. These partnerships are an efficient means of reducing cost and streamlining management of international programs.

Through FIC's **AIDS International Training and Research Program (AITRP)**, NIH-supported investigators work cooperatively in Africa, Asia, and Latin America to understand the full threat of the AIDS epidemic and develop tools for treatment and intervention. The geopolitical, as well as scientific benefits of these partnerships are significant. Many of our AIDS trainees represent the current and future scientific leadership of their countries. In partnership with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), and other NIH institutes, AITRP has become a leading source of AIDS research advances derived from international studies. Through studies of populations in regions of the world where the burden of the AIDS virus is greatest, we have increased our understanding of the virulent properties of HIV, risks of transmission, and devised strategies for prevention and therapy.

One important study opens up a new path for vaccine development. In follow-up of studies reported to the Subcommittee last year, FIC-supported researchers from Harvard University working in Senegal learned that a prior infection with HIV-2 (a less common, less virulent form of HIV-infection) protected against subsequent infection with the deadly HIV-1. These findings appeared in the journal Science on June 16, 1995. There is a key historic precedent for the importance of examining the cross-reactions between similar virus types. The discovery 200 years ago that cowpox infection protected milkmaids from smallpox became the basis for a vaccine that eradicated smallpox.

And here at home, a foreign research fellow supported by the FIC at the Los Alamos National Laboratory contributed to a landmark study to determine how rapidly HIV replicates and mutates, enabling the virus to evade the body's immune mechanisms. These findings were reported in the journal Nature on January 12, 1995. The results are described in the NIH Overview in the Congressional Justification. The finding has altered the way AIDS drugs are now designed and evaluated. An FIC-supported research fellow at UCLA helped to describe the disappearance of HIV from an infant infected by its mother--a noteworthy event that suggests the potential of the immune system to control or eliminate the virus. These findings were reported in The New England Journal of Medicine, on March 30, 1995.

FIC's HIV/AIDS research and training effort is a successful approach that can be applied to respond to other global health threats. With the support of Congress, FIC has broadened its efforts to meet three interrelated health priorities that require international cooperation--new and emerging infectious diseases, environmental health, and population growth. FIC's objective is to create strategic international research partnerships in these areas, as it has with HIV/AIDS, and continue to exert a compelling leadership role for the United States.

The International Research and Training Program on New and Emerging Infectious Diseases begun just this year supports cooperative research and training in regions of the world that are the potential origin of new epidemics, employing new molecular and analytic tools in their study. Knowledge gained may support the development of a global research sentinel system capable of detecting and containing future epidemics. The program represents a partnership with the NIAID and the Centers for Disease Control and Prevention (CDC).

The International Training and Research Program in Population and Health supports research to improve reproductive and neonatal health care and demographic capabilities in countries where population growth impedes economic development and quality of life. The goal is to better understand the social and behavioral determinants of population growth and develop public health interventions through research. The program was launched in partnership with NICHD.

The International Training and Research Program in Environmental and Occupational Health positions the U.S. to work cooperatively with regions of the world with relatively high levels of contaminants in the ambient environment and the workplace. Important data on the effects of carcinogens, such as dioxin, on human health are derived from international studies. With the application of new scientific methods, the effects of environmental agents on human health will be examined and interventions could be devised to reduce health risks. This program was launched in cooperation with the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health of the CDC.

The health consequences of environmental degradation also include the potential loss of valuable medicinal products derived from nature. For centuries, plants have been the source of medicines such as digitalis for heart disease and quinine for malaria. In the United States, more than one-quarter of the most prescribed pharmaceutical drugs have their origin in natural products. Yet only a small fraction of the world's biological wealth has been studied for potential therapeutic benefit.

The International Cooperative Biodiversity Groups Program, supported and administered by FIC, is designed to discover new drugs from the earth's biological diversity. In addition, strategies are pursued to preserve biological diversity and promote economic growth through drug discovery and development. In its first two years, over 2,000 species of plants and insects have been examined for their potential therapeutic properties. About 120 samples have been shown to be biologically active. These are now being tested as candidate drugs against certain cancers and viral diseases, malaria and degenerative neurological disorders. This pioneering program has influenced resource management policies in several participating countries, and has served as a case-study in international treaty discussions. The program is cost-shared by several NIH components including the FIC, the National Science Foundation, the U.S. Agency for International Development, and U.S. industries. It demonstrates the potential of pooling expertise and resources across the public and private sectors in pursuit of common scientific objectives.

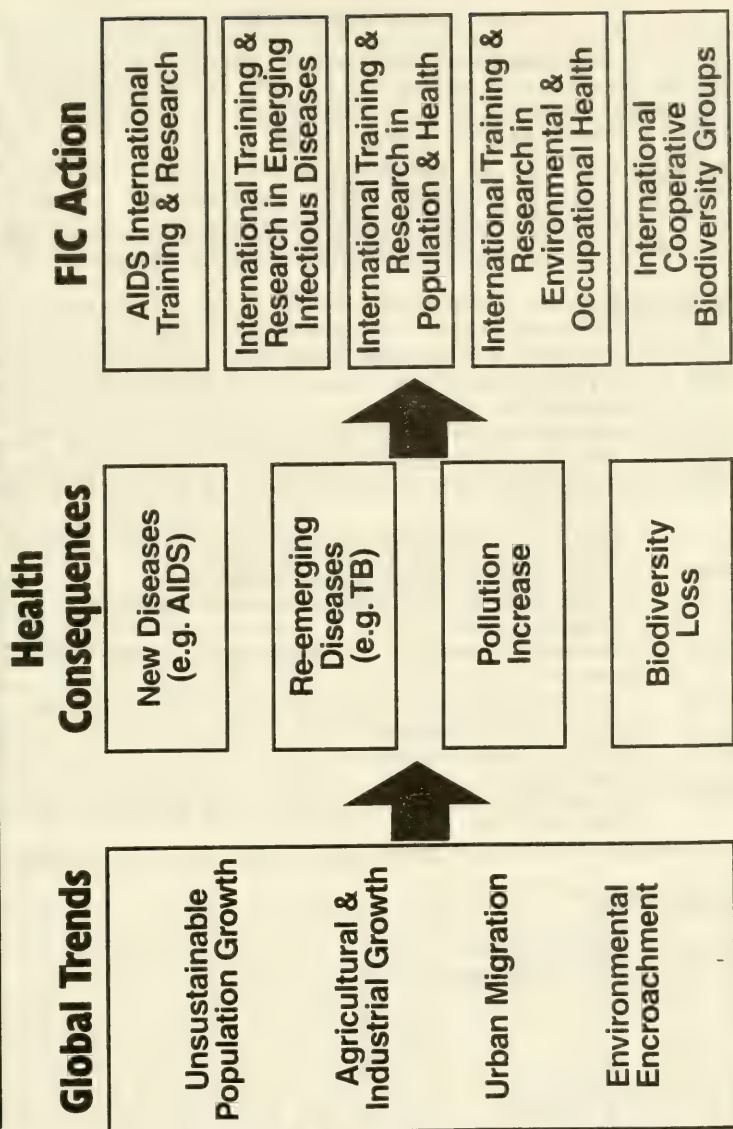
As resource needs increase due to the complexity of scientific challenge, international cooperation presents an important means to share costs and to avoid duplication. In collaboration with research agencies in the United Kingdom, France and nations in Africa, the FIC is leading efforts to accelerate research on the prevention of malaria by sharing resources, facilities or field sites, and exchanging scientific personnel. If successful, this pilot project will expand to other high priority public health areas. The FIC also has negotiated a postdoctoral exchange program for American and Japanese biomedical scientists, supported in its entirety by the Japan Society for the Promotion of Science. The program enables the U.S. to benefit from new technologies pioneered in Japanese laboratories in such areas as protein engineering and advanced instrumentation.

The basis for these programs and new directions is the FIC comprehensive long-range plan, developed in consultation with NIH components, the FIC Advisory Board and the broader scientific community. With the support of Congress, FIC has been able to implement its major planning initiatives in a rapid, eighteen-month timeframe.

Our namesake, John E. Fogarty, served as chairman of this Subcommittee and is part of a continuing lineage of Congressmen who have made NIH an international leader, not only in the quality of its research, but through its humanitarian interactions with over one hundred nations. In John Fogarty's words, "our international programs more properly can be characterized as enlightened self-interest, since it can be amply demonstrated that we receive as well as give." As the component of the NIH legislated to improve health through international cooperation, FIC is cognizant of its special obligations and partnership with the American public. Our shared purpose is to ensure that the U.S. scientific community is prepared to meet current and emerging global health threats. The cooperative pursuits of the international community of scientists are key to the future health of the world's citizens and environment, to economic prosperity and global security.

Thank you Mr. Chairman. Our FY 1997 budget request is \$15,790,000. I will be pleased to answer any questions.

FIC Action Against Global Health Threats



CURRICULUM VITAE

Name: SCHAMBRA, DR. PHILIP E.

Date & Place

of Birth: November 8, 1934. Saginaw, Michigan

EDUCATION: 1956 B.A., Rice University
 1961 Ph.D., Yale University
 1961-1963 Postdoctoral, Institut für Strahlenbiologie, Karlsruhe, Germany
 1964-1966 Postdoctoral, University of California, Berkeley

Professional History:

1956-1958 Research Assistant, Biophysics Department, Yale University.
 1958-1961 Predoctoral Fellow, National Cancer Institute, Biophysics Department, Yale University.
 1961-1963 Research Associate, Institut für Strahlenbiologie, Karlsruhe, Germany.
 9/64-2/65 Instructor, Department of Medical Physics, University of California, Berkeley.
 1964-1967 Research Biophysicist, University of California, Berkeley. NASA Research Fellowship.
 1966 Laboratory Director, National Science Foundation Summer Institute in Radiobiology, University of California, Berkeley.
 1967-1968 Grants Associate, National Institutes of Health.
 1968-1971 Budget Examiner, Office of Management and Budget, Executive Office of the President.
 1971-1974 Staff Member, Council on Environmental Quality, Executive Office of the President.
 1974-1980 Associate Director for Interagency Programs, National Institute of Environmental Health Sciences, NIH.
 1980-1984 Chief, International Coordination and Liaison Branch, Fogarty International Center, NIH.
 1984-1988 Science Attache and PHS International Health Representative, U.S. Embassy, New Delhi, India.
 1988-Present Director, Fogarty International Center, National Institutes of Health.

Honors and Awards:

1984 NIH Merit Award
 1989 PHS Superior Service Award

REVIEW OF INTERNATIONAL PROGRAMS

Mr. PORTER. Dr. Varmus, if we could start with you. Can you tell us about the external review of the NIH international programs that you announced in February? What led you to ask Joshua Lederberg to lead such an effort, and what goals have you set for the panel?

Dr. VARMUS. Mr. Porter, the issue is how we can best go about administering our international efforts. There is certainly no intention whatsoever to retreat on the international health science front. On the contrary, if anything, I would like to see us increasing our efforts.

But I'm increasingly aware of the efforts being made by individual institutes to develop their international programs, often in collaboration but, not necessarily in collaboration with the Fogarty Center. What I'm asking the panel to do is to look at what NIH does abroad. In total, we spend nearly \$180 million per year in international programs of all kinds. We need to ask whether the administrative activities are properly located as they are, or whether there should be some rearrangement of the way in which we administer our international affairs.

Dr. SCHAMBRA. Mr. Porter, if I might just add to Dr. Varmus' comment. Let me say that it is an initiative that we in the Fogarty Center welcomed very much. As you know, in the last few years, we've completed the development of a long range plan for the first time in the Fogarty Center's history, an important part of which was a commitment to review our programs and our directions, depending upon new and changed circumstances.

This study, in fact, which will be headed by Dr. Lederberg, is very much consistent with that philosophy and that design, and we're looking forward to not only working with the committee as it develops its work, but to its recommendations to all of us.

BIOMEDICAL RESEARCH FUNDING IN OTHER COUNTRIES

Mr. PORTER. Dr. Schambra, I wonder if you could describe for us the structure of biomedical research funding in other countries. My understanding is that research in most other countries is directed centrally, conducted in national laboratories rather than being university-based and investigator-initiated. Is that true for all the developed countries except the United States?

Dr. SCHAMBRA. I think, by and large, that description is quite accurate. I think the United States has led the way in demonstrating that investigator-initiated and peer-reviewed research is the most effective way to go, by picking the best ideas of individual scientists, wherever they may reside, particularly looking to the academic community, where you have teaching and training, along with research, and the unfettered academic atmosphere that encourages pursuit of good ideas, supported by an agency like the National Institutes of Health.

Mr. PORTER. If we've been so successful, why hasn't our model been replicated in other developed countries?

Dr. SCHAMBRA. Well, I was just going to add that. What we're seeing is in fact a ratification of the approach of the United States and the NIH, and a tendency in other parts of the world to go in

this direction. I think most prominently we've seen it in the former Soviet Union and Eastern Europe, where decisions on funding scientific activity were made top down, where the budget was allocated to the ministries and the ministries to the institutes and the institute directors to the scientists. Now what we're seeing in nearly all of these countries is the creation of organizations very similar to the NIH and the National Science Foundation and their decision making process.

BIODIVERSITY INITIATIVE

Mr. PORTER. I continue to be very interested in your biodiversity initiative. I would think that the pharmaceutical companies would have every incentive to invest heavily in the testing of natural products for their clinical usefulness. How much do they contribute to your effort and how much do they invest independently?

Dr. SCHAMBRA. Based on the most recent information that we have, from the first two years of the program on which we have data, U.S. industry has contributed about \$500,000 in total, divided between in-kind contributions and cash contributions on the part of these five biodiversity cooperative grants that are operational. The pharmaceutical company investment overall in drug development is a much more significant figure, of course, running into the billions of dollars. I don't happen to know what that figure is off-hand, but I'll be happy to provide it for the record.

[The information follows:]

BIODIVERSITY INITIATIVE

According to annual surveys conducted by the Pharmaceutical Research and Manufacturers of America (PhRMA), it is estimated that during 1996, U.S. pharmaceutical companies will spend \$12.8 billion on domestic research and development and an additional \$2.9 billion abroad, for a total of \$15.7 billion. Because of the way in which the industry maintains financial records, PhRMA cannot estimate the proportion that is spend on research and development of drugs from natural products.

MIDDLE EAST

Mr. PORTER. Are you involved in the Middle East cancer initiative that Dr. Klausner described?

Dr. SCHAMBRA. Yes, we are. In fact, we've had over the years a very close working relationship with the Cancer Institute, most recently going back a few years in which we assisted them in developing the Middle East Cancer Society. I guess it was the establishment of a society of academicians and scientists throughout the Middle East to begin to share knowledge and information about their programs in cancer, which has now been capitalized upon by Dr. Klausner's very commendable initiative to have the health ministries of the region get together and develop a cancer consortium.

Our role has been, because this is part of a much larger process going on in the Middle East, which is obviously a very sensitive area to the United States and a very active area in our foreign policy, making sure that the proposed cancer consortium fit into the overall strategy for the Middle East, working with the State Department and we've gone on beyond that, because the State Department has, as I'm sure you know, funds set aside to support Middle East regional cooperation. We are now working with the Cancer Institute and the State Department to try to acquire some

of those funds to support the activities that Dr. Klausner has initiated in the Middle East consortium.

Mr. PORTER. I personally think that this effort goes far beyond the obvious one of advancing the cause of cancer research in that region. Getting countries that often don't cooperate with one another working on something together I think is very, very positive, and we ought to do everything we can to encourage it.

Dr. SCHAMBRA. Absolutely, Mr. Porter, and I think it's an excellent model to be used in other areas. And it's one of the reasons that, as Dr. Klausner mentioned, we're now looking at certain parts of Asia where there's a long history of enmity between certain countries. We think that they may be able to be brought together for some common good, like the cancer consortium.

Mr. PORTER. Maybe we can conduct our future competitions on the research playing field instead of the war field. Let's hope.

Dr. VARMUS. As you know, Mr. Porter, the National Academy of Sciences has also been instrumental in bringing together the academies of sciences in the Middle East for meetings in Washington. And the discussions have ranged beyond biomedical research to issues of water conservation and agriculture and other very important issues.

Mr. PORTER. That's wonderful.

Mr. Hoyer?

Mr. HOYER. I don't have any questions, Mr. Chairman.

Mr. PORTER. Mr. Stokes?

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Schambra, welcome to our subcommittee.

Dr. SCHAMBRA. Thank you, Mr. Stokes.

VITAMIN A

Mr. STOKES. Last year, Dr. Schambra, we discussed the role that Vitamin A might play in helping to control the transmission of the HIV virus, and the interesting results from studies regarding the differences in the infectivity of the virus. What progress can you report to us here today regarding that research?

Dr. SCHAMBRA. Well, I'm pleased to say that as a result of those studies, which were carried out in part by our grantees under the AIDS International Training and Research Program, that working with the Child Health Institute and our grantees, we have initiated a clinical trial in I believe it's Uganda to see whether nutritional supplementation of mothers' diets and infant's might in fact have an impact on both the transmission of HIV and survival of the infant infected with the HIV virus.

Mr. STOKES. Do we have several clinical trials going on in this area?

Dr. SCHAMBRA. I think that there is one clinical trial, but I will confirm that for the record.

Mr. STOKES. Okay. I would appreciate that.

[The information follows:]

VITAMIN A

Through the AIDS International Training and Research Program, the FIC is involved with the National Institute of Child Health and Human Development in supporting two trials in Tanzania and Malawi involving Vitamin A supplementation to

the mother before delivery and a trial in Uganda that provides supplementation to the infant.

NEW AND EMERGING INFECTIOUS DISEASES

Mr. STOKES. Doctor, as you know there is considerable concern regarding the increase in new and the reemergence of once-controlled infectious diseases. Worldwide infectious diseases as a group are one of the leading causes of death. What are some of the major activities underway between the United States and its international biomedical research partners to address this worldwide public health problem?

Dr. SCHAMBRA. Well, this has been a very high priority issue, not only for the Fogarty Center and the NIH, but indeed for the current Administration. The President's National Science and Technology Council and its Committee on International Science, Engineering, and Technology, under the direction of Undersecretary of State Tim Worth, did a major inter-agency study looking at the question of new and emerging infectious diseases, and how to organize and orchestrate a cooperative approach internationally to this matter.

We have in fact proposed to start out very modestly this fiscal year, with funds made available by Congress, to initiate, the International Training and Research Program in new and emerging infectious diseases that would be modeled on our already longstanding and proven AIDS International Training and Research Program. I'd say that's been our principal contribution the past year on that topic.

HIV-I AND HIV-II

Mr. STOKES. Doctor, I understand that individuals with HIV II appear to have some protective mechanism against becoming infected with HIV I. How close are we to understanding, and in some cases unraveling, this critical difference between these two forms of HIV? What major work is underway here in the United States to study these differences?

Dr. SCHAMBRA. Mr. Stokes, that is one of the findings that I mentioned last year in my testimony that came from one of our grantees. Since I am not an expert on AIDS, I think I would have to refer to Dr. Fauci or Dr. Paul. But to give you an answer to that, I will, if I may, provide it for the record.

Mr. STOKES. That would be fine.

[The information follows:]

HIV-1 AND HIV-2

HIV-1 and HIV-2 are genetically related but distinct viruses, with HIV-2 mostly confined to West Africa. Although transmitted by the same routes, HIV-2 is less easily transmitted than HIV-1, and individuals infected with HIV-2 remain asymptomatic longer and HIV-related disease progresses more slowly than in individuals infected with HIV-1. Recent studies have demonstrated that commercial sex workers in Dakar Senegal infected with HIV-2 either before or during the study had a lower incidence of HIV-1 infection than HIV-2 seronegative women—prior infection with HIV-2 appear to protect them from subsequent HIV-1 infection. However, the analogous "cross-protection" was not observed for infection with HIV-2 in women previously infected with HIV-1.

The issue of cross-protection is the subject of continued scientific debate and investigation to confirm or refute this observation. In addition, future studies will examine potential mechanisms of cross-protection. One hypothesis is that the protec-

tion is a result of cross-relative immunity to portions of HIV-1 that are genetically similar to HIV-2 but that because of differences between HIV-1 and HIV-2, individuals produce a different immune response when infected with HIV-2 than when infected with HIV-1. Further study of the mechanisms of HIV-1 immunity in this context may provide information relevant to the development of HIV vaccines.

Much of the work on HIV-2 is being done in West Africa because of the prevalence of HIV-2 in that region. Supported by NIAID and FIC, researchers from Harvard University in the U.S. are continuing collaborations with researchers in Senegal to further investigate the differences between the two types of HIV and, in particular, the implications of cross-protection. Ten papers resulting from this collaboration on HIV-2 and other areas of AIDS research were reported at the IX International Conference on AIDS and STD in Africa held in December in Uganda.

MINORITIES IN INTERNATIONAL RESEARCH

Mr. STOKES. Dr. Schambra, as you know, each year I've asked you for an update on the Center's diversity initiative with respect to the participation of minorities in international research. What progress can you report to us this year on this initiative?

Dr. SCHAMBRA. Well, I'm very pleased to say, Mr. Stokes, now we have been through our third funding cycle in this program, a total of 33 grants have been awarded involving 57 colleges and universities throughout the country, of which 18 are historically Black colleges and universities. Through the first two years of the program on which we have complete data, a total of 511 minority students and faculty have participated in the international research activities.

That is, they've gone abroad to work in foreign laboratories, to work in foreign field sites, and come home to tell us about the marvelous experiences and the significant contributions that they've made to biomedical science. Of this number, nearly 60 percent were African-American, about 40 percent were Hispanic-American, 3 and a half percent were Native American, 1 and a half percent were Asian and Pacific Islander and 1 percent other.

For the past four years, we've held network meetings, as we call them, meetings of the principal investigators under these programs, to bring them together to share their problems and their successes with one another and with us, to try to make this program much more effective and efficient, to in fact even work across institutional lines to identify students and faculty that might participate in each others' programs.

One of the major, and I think very positive features, of the program has been the establishment of consortia between universities and colleges where we will have maybe a large university that might be a typical majority university, but with a significant minority population, working up arrangements with minority institutions in their regions, such as the University of Maryland has with eastern shore colleges. This has been, again, a very positive experience for these institutions, going way beyond the immediate goals of the Minority International Research and Training Program.

Mr. STOKES. You've done a good job in this area, and I appreciate it. Thank you, Dr. Schambra.

Dr. SCHAMBRA. Thank you, Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

PARTNERSHIP FUNDING

Mr. PORTER. Dr. Schambra, your testimony mentions that nearly 60 percent of the funds you manage come from elsewhere in the Federal Government. How much does this total, and who are the major Government agencies that turn money over to the Fogarty Center? What do you do to encourage the development of these partnerships?

Dr. SCHAMBRA. In regard to the question of the total that we will be spending, or expect to spend in the current fiscal year, its roughly \$34 million. Of that, about \$14 million is directly appropriated to the Fogarty Center. So roughly \$20 million comes from other than the Fogarty Center's direct appropriation. Approximately \$10 million—\$9 million to \$10 million—of that comes from the Office of AIDS Research, for our AIDS International Training and Research Program. About \$8 million comes from the Office of Research on Minority Health, for our Minority International Research and Training Program.

I mentioned earlier other training programs, on population for example, where we share funding with the Child Health Institute, and on environmental and occupational health, where we share funding and administrative functions with the National Institute of Environmental Health Science and CDC's NIOSH. And then of course, the biodiversity program, which was quite innovative and creative in going beyond just the National Institutes of Health and Public Health Service, and involved not only NIH institutes but the National Science Foundation and the U.S. Agency for International Development.

It has been a fundamental principle during my eight years as Director of the Fogarty Center that the programs we undertake scientifically will be those that are supported in principle and in practice. By that I mean helping us design the programs and perhaps even co-funding the programs, by those agencies that have the in-depth scientific expertise to certify that in fact these are scientifically meritorious programs, even to the point where in many cases we used the review committees established by the institutes to do the peer review of the proposals we receive.

MALARIA RESEARCH

Mr. PORTER. Using the example of malaria research and control, can you describe how your Center's efforts relate to the work being done elsewhere in the Public Health Service? Obviously, the Allergy Institute at NIH and CDC have a major involvement in research and control activities. What additional component does Fogarty Center bring to this activity?

Dr. SCHAMBRA. Mr. Porter, like the programs that I've mentioned and that are shown on the right hand side of the chart, our recent interest in malaria has been stimulated by several events. One going back a few years in which we have had dialogue on and off with our partners in France and in the United Kingdom, in particular, about how we might better coordinate our international scientific activities, pool our resources and facilities, make dual use or multiple use of the field sites that each of us have developed.

And so what we decided to do was to bring together representatives of these institutions, along with those from the NIH, last July, for a meeting in which we talked about what possibilities there were for us working together in a collaborative mode, a more strongly interrelated mode. We were very grateful that Dr. Varmus could spare the time to spend a whole day with us during that meeting. And as an outcome of those discussions, it was agreed that maybe the best way to proceed with advancing this concept of international sharing and cooperation would be to pick a particular health problem that we could focus on and focus on where it had a significant impact in Africa.

Dr. Varmus suggested that because of the latest scientific advances in the molecular biology of the malaria parasite and vector, malaria would be a good problem to study. And so indeed, we will hold, on Friday and Saturday of this week, a planning meeting of representatives from around the world and the NIH. Dr. Varmus will be able to attend part of it. Dr. Kirschstein will represent him on the next day.

We will plan a conference to be held some time later this year or next, focused on what the world scientific community might be able to do additionally to attack the problem of malaria. This will be a strategically focused meeting, not just simply a reporting of the latest scientific results, but rather focused on what concretely we can do to advance the state of science and the state of the art against the disease of malaria, which is killing 2 to 3 million people a year in Africa alone.

Mr. PORTER. Dr. Schambra, we thank you for the fine job that you're doing at the Fogarty Center. We thank you for your excellent testimony today, and appreciate your coming before the panel.

Dr. SCHAMBRA. Thank you, Mr. Chairman.

Mr. PORTER. Thank you so much.

The subcommittee will stand in recess until 2:00 p.m. this afternoon.

[The following questions were submitted to be answered for the record:]

Questions Submitted by the Subcommittee

Number of Minority Researchers

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Center is doing to increase the number and involvement of African Americans and other minority research investigators and the participation of HBCUs in the activities which are under the Center's purview?

Dr. Schambra: We are very pleased with the interest expressed in and the success of our Minority International Research Training Program (MIRT). In FY 1995, with additional funds from the NIH Office of Research on Minority Health, we funded seven new MIRT awards for a total of 33 awards. This resulted in a network of 57 U.S. colleges and universities of which 18 are historically black colleges and universities (HBCUs). Of the 18 HBCUs, seven have received direct awards and 11 are participating through consortia arrangements. For the first two years of the program, a total of 511 minority students and faculty have participated in research projects abroad.

As you may recall, the MIRT Program provides grant awards to U.S. institutions to support innovative approaches to research training with a focus on 1) encouraging qualified minority students to pursue post-baccalaureate degrees and consider research careers in the biomedical or behavioral sciences; 2) broadening minority student research training to include international issues and concerns; and 3) assisting the next generation of scientists to work effectively in the global environment by establishing international linkages on several levels--linkages between U.S. students and foreign scientists at centers of biomedical and behavioral research abroad, between U.S. minority scientists and foreign scientists abroad, and between minority and minority-serving institutions and research institutions operating abroad. Linkages are also encouraged between U.S. institutions for the purpose of facilitating minority student transitions from baccalaureate degree programs at non-research intensive institutions (i.e., a number of Historically Black Colleges and Universities and some Hispanic serving institutions) to graduate programs at research intensive institutions. The program is also unique in its potential for ensuring diversity among the U.S. student population represented overseas, in particular, since minority students are less likely than their majority counterparts to participate in study abroad programs. At last count 30 HBCUs and Hispanic-serving institutions combined were participating as direct grant recipients or as part of consortia arrangements under MIRT programs, an overall increase of 3 institutions compared to last year.

The Fogarty International Center in collaboration with the Office of Research on Minority Health has expanded the MIRT Program in three areas. A foreign mentor visitation component has been added, the participation of minority medical students with a strong interest in pursuing biomedical or clinical research is encouraged, and a limited number of competitive pilot research projects will be supported. Expanding participation to include medical students will increase the number of minority students

who are encouraged to consider research careers. The pilot research projects are intended to encourage research collaborations between MIRT program faculty participants and scientists abroad in particular in (but not limited to) areas that are relevant to minority health issues. The research supplements will be similar to the Fogarty International Research Collaboration Awards Program where awards are made to U.S. institutions to support collaborative research between U.S. investigators and their counterparts abroad. The foreign visitation component provides support for approved foreign mentors to participate in training activities and/or to conduct research in MIRT institutions for periods up to 12 weeks per year in order to reach a greater number of minority students and to facilitate collaborative research under the MIRT program. In addition, with the recompetition of the first set of awards, we plan to extend the period of performance from three years to four years.

Collaborative Efforts with Office of Research on Minority Health

Mr. Stokes: What collaborative efforts are underway with the Center and the Office of Research on Minority Health? Are there specific projects in the Center that are funded totally by the Office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Schambra: The original arrangement was that the Office of Research on Minority Health (ORMH) would provide full funding and the FIC would provide the programmatic management of the MIRT Program. The following table provides information on the MIRT programs and funds provided by the ORMH.

MIRT PROJECTS				
INSTITUTION	PROGRAM DIRECTOR	PERFORMANCE PERIOD		FY 1995 FUNDING (\$ IN 000)
Albany State College	Lockley	25-Sep-93	24-Sep-96	80,891
University of California, Irvine	Villarreal	25-Sep-93	24-Sep-96	134,633
University of California	Ortiz	25-Sep-93	24-Sep-96	270,202
University of New Mexico	Glew	30-Sep-93	29-Sep-96	161,956
University of Maryland at Baltimore	Warnick	25-Sep-93	24-Sep-96	444,844
The City College of CUNY	Boto	25-Sep-93	24-Sep-96	242,649
Johnson C. Smith University	Sutton-Haywood	25-Sep-93	24-Sep-96	201,386
Winston-Salem State University	Atkinson	28-Sep-93	27-Sep-96	231,147
Barry University	Frei	25-Sep-93	24-Sep-96	107,084
University of Michigan	Lozoff	25-Sep-93	24-Sep-96	527,843
University of Arizona	Ribeiro	30-Sep-93	29-Sep-96	241,432
University of Pittsburgh	Tull	01-Sep-94	31-Aug-97	97,701

Howard University	Anderson	01-Sep-94	31-Aug-97	367,502
Howard University Cancer Center	Adams-Campbell	25-Sep-93	24-Sep-96	396,078
Meharry Medical College	Hill	30-Sep-93	29-Sep-96	281,100
Hampton University	Urasa	01-Sep-94	31-Aug-97	102,793
SUNY/College at Old Westbury	Stefano	25-Sep-93	24-Sep-96	91,362
University of Puerto Rico	Craig	25-Sep-93	24-Sep-96	100,057
California State University, Fullerton	Weber	01-Sep-94	31-Aug-97	197,919
University of Washington	Williams	01-Sep-94	31-Aug-97	345,688
University of Alabama	Onolemhemen	01-Sep-94	31-Aug-97	102,606
Michigan State University	Petropoulos	01-Sep-94	31-Aug-97	381,937
University of Illinois at Chicago	McElmurry	01-Sep-94	31-Aug-97	194,048
University of California, Los Angeles	Galal	01-Sep-94	31-Aug-97	282,844
University of Pennsylvania	Winegrad	01-Sep-94	31-Aug-97	397,862
University of California, Los Angeles	Lopez	01-Sep-94	31-Aug-97	163,536
San Diego State University	Pozos	30-Sep-95	29-Sep-98	235,165
Oakwood College	Gwebu	30-Sep-95	29-Sep-98	66,865
Texas A&M University	Sis	20-Sep-95	19-Sep-98	188,083
Cornell University	Rodriguez	20-Sep-95	19-Sep-98	148,278
University of Alabama at Birmingham	Alvarez	20-Sep-95	19-Sep-98	317,056
San Francisco State University	Orrego	30-Sep-95	29-Sep-98	274,559
Duke University Medical Center	Hamilton	30-Sep-95	29-Sep-98	222,894
TOTAL				\$7,600,000

Mr. Stokes: Are there specific projects that are co-funded by the Center and the Office, and if so, why and which are they? Also for the record, provide a complete listing of these projects, include their period of performance, and the percentage and the amount of funding provided by the Institute and the Office.

Dr. Schambra: FIC provides funding for U.S. minority health science students to receive research experiences under its AIDS International Training and Research Program at a level of approximately \$300,000 per year. This special effort initially began with support from the Office of Research on Minority Health.

JUSTIFICATION OF THE BUDGET ESTIMATES

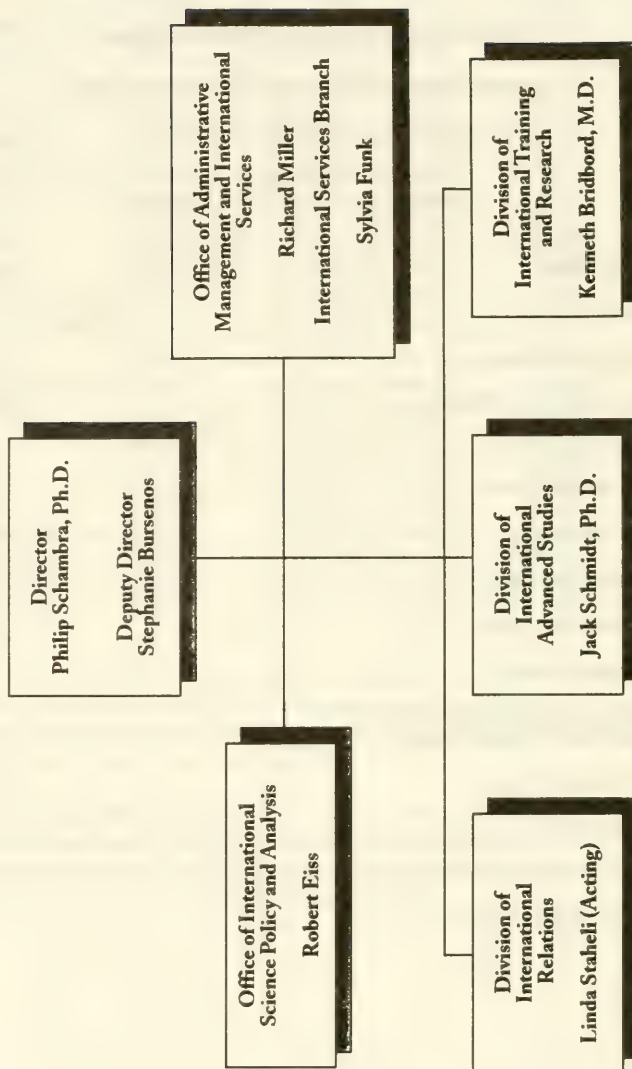
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

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NATIONAL INSTITUTES OF HEALTH
John E. Fogarty International Center
Organizational Chart



NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

For carrying out Sections 301 and 307 and title IV of the Public Health Service Act with respect to the John E. Fogarty International Center, \$15,790,000.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$14,697,000	\$25,313,000	\$15,790,000
Reduction in accordance with P.L. 103-333.....	-30,000	—	—
Reduction in accordance with P.L. 104-19.....	-21,000	—	—
Subtotal, Adjusted Appropriation.....	14,646,000	25,313,000	15,790,000
Real Transfer to:			
Other NIH Institutes through the NIH Director's one percent transfer authority.....	-13,000		—
Comparative transfer from:			
National Institute of Mental Health for one position.....	17,000	35,000	—
Comparative transfer to:			
Office of AIDS Research, NIH for NIH activities.....	—	-9,694,000	—
Subtotal, adjusted budget authority.....	14,650,000	15,654,000	15,790,000
Unobligated balance, lapsing.....	-12,000	—	—
Total, obligations.....	14,638,000	15,654,000	15,790,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1995 - \$11,414,000; FY 1996 - \$11,100,000; and FY 1997 - \$11,100,000.

Also excludes funding for HIV activities: FY 1995—\$9,108,000; FY 1997 - \$9,757,000, included
in Office of AIDS Research, NIH.

Justification

John E. Fogarty International Center
for Advanced Study in the Health Sciences

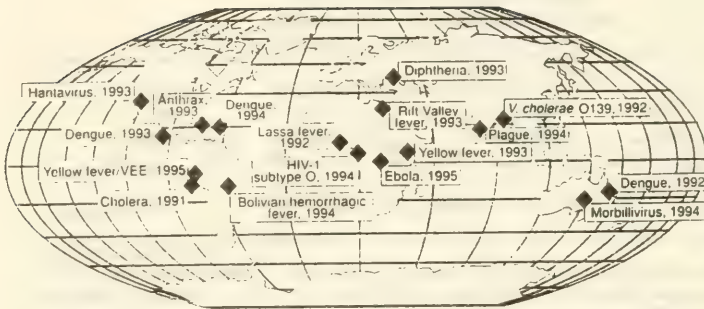
FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
68	\$14,650,000	76	\$15,654,000	76	\$15,790,000	---	\$136,000

This document provides justification for the FY 1997 Non-AIDS activities of the Fogarty International Center (FIC). Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The FIC was established by Congress to advance the health of the people of the United States through international scientific cooperation. Foremost is the need to protect American citizens from health threats that arise from abroad. These include the emergence or resurgence of infectious diseases such as AIDS, Ebola and cholera, increasing occurrences of antibiotic resistant microbes, and the transnational spread of pollution.

In partnership with the NIH research institutes, the FIC carries forward the founding mandate of NIH -- to discover the causes and solutions for diseases that know no national boundaries. In the last 50 years, biomedical research has become an intense international pursuit to discover new causes of disease across the spectrum of medicine -- heart disease, cancer, infectious diseases. These include those of immediate domestic concern, such as AIDS, and emerging diseases in far away places in Central Africa such as Ebola virus. International collaboration and communication has mobilized the worldwide scientific community to meet these threats and has accelerated the pace of discovery.

The AIDS pandemic is a cautionary tale. It demonstrates the continuing risk of diseases that emerge as a consequence of microbial adaptation, human encroachment on natural ecosystems and rapid social changes. These include multi-drug resistant tuberculosis, Hantavirus respiratory syndrome, Ebola virus and other hemorrhagic fevers. Moreover, the speed and extent of international travel can quickly transform a local disease outbreak into a global epidemic. All of these events can and will happen again. New knowledge gained through research is our only defense. The following chart illustrates the increasing international threat of new infectious diseases.



For various reasons chronic and degenerative diseases have become a major health burden to people the world over. The causes are diverse and complex. Exposures to environmental carcinogens and abused substances at the earliest stages of life increase the risk of neurodevelopmental disorders. As the population ages, a greater number of people will develop senile dementias such as Alzheimer's disease, as well as age-related disorders such as arthritis, hearing loss and blindness.

The FIC is responding to public health challenges of global impact by linking scientists and laboratories worldwide. By funding cooperative research and training programs between Americans and their counterparts in the developing world, FIC ensures that a highly trained cadre of basic and clinical investigators exists in those countries which will participate in research to develop and test new drugs, vaccines and other interventions.

HIV/AIDS and Emerging Infectious Diseases

With FIC support, a global network of laboratories and clinics from Boston to Brazil to Uganda to India to Thailand, and dozens of other sites, has been mobilized to combat the worldwide AIDS epidemic. The AIDS virus has undergone genetic modifications during its global dissemination. Furthermore, differences in cultural, medical and sexual practices among countries affected by HIV have influenced the course of the epidemic. All of these factors must be considered in research on prevention strategies and vaccine development.

FIC is the world's leading source of international research training related to HIV/AIDS. FIC efforts in cooperation with the National Institute of Allergy and Infectious Disease, the National Institute of Child Health and Human Development and other NIH components, have led to important research results in FY 1995.

Oftentimes in science nature by itself performs an experiment which opens a new line of investigation, and this occurred recently in Senegal. FIC-supported scientists from Harvard observed the occurrence of HIV-1 infection in individuals, the cause of devastating fatal AIDS, simultaneously with HIV-II infection, a much less virulent form of the virus. They

were surprised to learn that prior infection with the mild HIV-II protected against subsequent infection with the deadly HIV-I.

Such information has important implications for HIV vaccine development. For example, the protective effect observed following HIV-II infection may be analogous to the discovery 200 years ago that mild cowpox infection protected milk maids from subsequent infection with the deadly smallpox. This experiment of nature became the basis for the worldwide use of cowpox vaccination to eradicate smallpox.

Another experiment of nature may uncover a natural immune mechanism that appears to have the power to halt the lethal progression of HIV infection. This concerns the transmission of HIV by infected mothers to newborn infants. Ten to 30 percent of infants born of HIV-infected mothers acquire HIV infection during or shortly after birth. An unexpected discovery, reported by an FIC-supported scientist, was the spontaneous disappearance of HIV in an infected infant. Studies are underway to determine the nature of the immune processes responsible for this favorable outcome. This may lead to new methods of immune therapy.

Other discoveries have directed research into new avenues for treatment and vaccine development. For example, an FIC-supported foreign scientist at the Los Alamos National Laboratory in collaboration with other scientists has made an unexpected discovery concerning the multiplication of the HIV virus in infected people. Earlier estimates suggest that very few virus particles were produced during the infection. This led to the conclusion that the virus infection was in a latent state. That view now has been reversed. The most recent analysis demonstrates that HIV generates a billion new viral particles each day. Its high replication rate gives rise to a large number of mutations and enables the virus to evade immune mechanisms and medical treatments. These findings have altered strategies for HIV drug design and evaluation.

The AIDS pandemic -- as well as the recent Ebola outbreak -- demonstrate the continuing need for international efforts to promptly detect and contain new diseases before they become global epidemics. In order to develop effective prevention strategies for new and emerging pathogens, research and related training is required on the complex interactions between humans and microbes and on the evolutionary and genetic factors that cause epidemics.

For this reason, in FY 1996, as directed by the Congress and in cooperation with NIAID, FIC will initiate a grants program for international research and training on new and emerging infectious diseases. Special emphasis will be placed on research and training in those regions of the world that are the potential origin of new epidemics, including the application of new molecular and analytic tools to detect these occurrences. In collaboration with other components of NIH, the CDC, and foreign counterparts, these efforts will become part of a global research sentinel system capable of anticipating and containing future epidemics.

Health and the Environment

New infectious diseases result from a broad pattern of ecological change, creating both real and potential health threats. Equally insidious health risks are presented by rising concentrations of industrial and chemical pollutants. Environmental toxins are increasingly recognized as important factors in the etiology of many health problems, including cancer, respiratory disease, kidney disease, autoimmune and developmental disorders. A related concern is the threat posed by the transnational spread of radioactive particles.

These hazards are global in scope and underscore the importance of international cooperation to assess the risk of environmentally-induced diseases, and to develop interventions to prevent diseases in populations exposed to known toxic substances. Strategic benefits for the United States derive from a global effort to confront environmental threats. Radiation released in the Chernobyl nuclear reactor disaster was a local health threat that spread across national boundaries as a consequence of radioactive fallout. Environmental pollution along the Mexican border poses a current threat in this hemisphere.

These global issues require transnational cooperation in research. To foster this endeavor, in FY 1995 the FIC launched an International Training and Research Program on Environmental and Occupational Health, developed and funded in cooperation with the National Institute of Environmental Health Sciences and CDC's National Institute for Occupational Safety and Health.

In its first year, the program awarded grants to seven U.S. institutions to cooperate with emerging democracies and developing nations in the former Soviet Union, Eastern Europe, Asia and Latin America.

Biodiversity and Medicine

For centuries, plants have been the source of medicines such as digitalis for heart disease and quinine for malaria. As a consequence of the depletion of flora and fauna--particularly the contraction of species-rich tropical rain forests--undiscovered medicines may be irretrievably lost. In the United States, an estimated one half of the most prescribed pharmaceuticals such as antibiotics have their origin in natural products. Yet only a small fraction of the world's biological specimens has been studied for potential therapeutic benefit.

To answer this need the FIC leads an interagency collaborative effort to discover new drugs from the earth's biological diversity. The International Cooperative Biodiversity Groups Program is operated and funded in partnership with NIH research institutes, the National Science Foundation, the U.S. Agency for International Development, and U.S. industries. In addition to drug development efforts, strategies are pursued to preserve biological diversity and promote economic growth through sustainable agriculture.

In its first two years, chemical compounds from over 2,000 species of plants and insects have been examined for their potential therapeutic properties. Substances extracted from 120 species have shown sufficient promise as potential drugs to warrant further investigation. There are candidates for certain types of cancer, viral diseases, malaria and

degenerative neurological disorders. This pioneering program has influenced natural resource management policies in several participating countries, and has served as a model case-study in international treaty discussions.

Health and Population

In part, global health problems are the result of a shifting demography, which places populations at risk of exposure to new infectious pathogens or environmental toxins. There may be a pernicious linkage between population growth and migration and the emergence of new diseases. Moreover, rapid population growth may hamper economic development, deplete resources and reduce quality of life in countries most affected.

In response, in FY 1995 the FIC launched the International Training and Research Program in Population and Health designed and co-funded in cooperation with the National Institute of Child Health and Human Development. Research activities will include development of a broader range of safe and reversible contraceptive methods--both temporary and long acting, and a new spermicide with anti-viral properties to prevent HIV transmission.

Improvements in prenatal health care through prevention research are essential to efforts to reach sustainable rates of population growth. This is because high death rates among children result in excess births to ensure that a desired number of children survive to adulthood. FIC's Population and Health Program will place emphasis on improvements in prenatal health care through prevention research. This includes studies on inadequate nutrition, toxemia and high blood pressure, which are frequent complications of pregnancy and present significant maternal and perinatal risks.

Now in its first year, grants were awarded to seven U.S. institutions to support cooperation with developing nations in Asia, Latin America and Sub-Saharan Africa.

Advanced Studies in Biology and Medicine

A key role of the FIC is to enable NIH to forge international partnerships and assist U.S. scientists to benefit from biomedical expertise worldwide. With the emergence of recombinant DNA technology, cell fusion and refinements of more classical techniques, biomedical science has become more complex and interdisciplinary, and progress is more rapid. The biomedical research enterprise has become an intense international pursuit to discover genes, protein sequences or signaling mechanisms that will enable scientists to reverse disease at the molecular level, or to shield or bolster the immune system. Ultimately, new molecular tools will enable scientists to unravel the molecular puzzle of cell differentiation and development.

As a consequence, global access to innovative concepts and research data has become a requisite for scientific discovery and progress. For example, recent discoveries of the genes associated with cystic fibrosis, Huntington's disease, and an hereditary form of colon cancer all resulted from international cooperation.

FIC's Scholars-in-Residence Program brings internationally eminent scientists to the NIH campus to address emerging challenges of modern biology. The International Research

Fellowship and Senior International Fellowship expand global research opportunities for U.S. institutions. The Fogarty International Research Collaborative Award lays the basis for continuing research partnerships between U.S. institutions and counterparts in emerging democracies and developing nations.

In FY 1995, a Scholar-in-Residence from Scotland and collaborators at the National Institute of Neurological Diseases and Stroke and the National Institute of Allergy and Infectious Disease provided insights into one mechanism that may underlie damage to nervous system cells caused by varicella-zoster virus (VZV) -- a herpesvirus. To assist in understanding the mechanism by which VZV causes disease, researchers infected cells from human nervous tissue with VZV *in vitro* and observed the resulting changes in cellular morphology and the expression of one key structural protein. A marked reduction was seen in expression of the protein, which suggests an underlying pathology that causes VZV to damage nerve cells. These findings may provide insights into the mechanisms by which other viruses cause disease in the nervous system.

A Fogarty-supported Scholar from Russia and collaborators at the National Institute of Child Health and Human Development created a technique that will provide insights into the mechanisms which underlie a range of biological phenomena, including metastasis of cancerous cells, the interaction of immune cells with virus-infected cells, and the interaction between growing neurons and their target tissues.

The technique combines methodologies for growing blocks of tissue *in vitro* with microscopic methods that enable scientists to view serial sections of the tissue block without physically sectioning the block. Individual cells or nerve processes, labeled with a fluorescent marker, are visualized as they interact with cells and tissues in a three-dimensional environment that more accurately reflects the *in vivo* state than previous methods have permitted.

Scientists at Stanford University and Masaryk University in the Czech Republic are studying the potential of a vitamin A derivative, retinoic acid, to stop the production of certain types of leukemic or cancerous white blood cells. A type of cancer known as acute promyelocytic leukemia responds favorably to relatively high doses of retinoic acid. Scientists believe this leukemia is caused by the production of a defective DNA binding protein (retinoic acid receptor) which regulates the ability of immature blood-forming cells to produce the various types of white cells found in blood. The presence of large concentrations of retinoic acid appears to improve the performance of the defective DNA binding protein, so that the normal complement of white blood cells can be produced. These results suggest that other types of leukemia may become responsive to retinoic acid therapy.

Scientists at the Wistar Institute in Philadelphia and the Czechoslovak Academy of Science are investigating how a subclass of cells in the immune system (natural killer cells), fight infection and offer protection against certain types of tumor cells by interacting with the sugars on the surface of the cells and then destroying them. This is a rapidly expanding scientific field and holds the potential for the development of innovative antitumor therapies using oligosaccharides (sugars consisting of less than ten sugar molecules).

International Science Policy and Analysis

A leading role of the FIC is to provide direction and guidance in the formulation of international policy issues which affect the biomedical research enterprise, and to develop scientific strategies to meet international research needs.

There is a continuing need to convene international experts to identify future research challenges and needs. In collaboration with research agencies in the United Kingdom, France and nations in Africa, the FIC is organizing an international conference on malaria. Specific objectives are to review the status and future directions in malaria research and training and identify potential collaborative projects. Emphasis will be placed on coordinating efforts to share costs, facilities or field sites, exchange scientific personnel, consult on current or planned research protocols, or otherwise work in concert.

This initiative is timely. It is now 40 years since the World Health Organization launched its plan for the global eradication of malaria. Yet the disease has proven intractable due to drug and insecticide resistance and differences in the biology of major malaria vectors. Biomedical research is critical to prevention and control of this infectious disease, which results in over 1 million deaths per year.

The FIC also has negotiated a new program with the Japan Society for the Promotion of Science that enables American postdoctoral scientists to work in Japanese laboratories on biomedical research projects of mutual interest. The program is entirely supported by the JSPS, and will enable the U.S. to benefit from new methods and technologies pioneered in Japanese laboratories in such areas as bioinstrumentation and cell biology.

Although FIC programmatic strategies are diverse, their design reflects a singular purpose: to bring to the American public the benefits of medical research wherever it occurs—improved health and quality of life.

FY 1997 Budget Overview

The FY 1997 budget request for the FIC's non-AIDS activities is \$15,790,000, an increase of \$136,000 over the comparable FY 1996 level of \$15,654,000. The request includes 76 FTEs, the same level as FY 1996. The budget request for FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

A total of \$3,790,000 is requested in Research Project Grants, an increase of \$100,000 over the comparable FY 1996 level of \$3,690,000. In the FY 1997 President's Budget Request, FIC support for research project grants (RPGs) would increase by 2.7 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community.

A total of \$5,922,000 is requested in Other Research Grants, reflecting an increase of \$100,000 over the comparable FY 1996 level of \$5,822,000. This increase will be used to enhance the FIC's Emerging Infectious Diseases Program initiated in FY 1996.

A total of \$6,078,000 will be available in the Research Management and Support mechanism, which reflects a decrease of \$64,000 over the comparable FY 1996 level of \$6,142,000.

The following table displays the funding by extramural program:

	1996	1997
Biodiversity Program	1,256,000	1,282,000
Population and Health Program	820,000	820,000
Environment and Health Program	750,000	750,000
Emerging Infectious Diseases Program	500,000	600,000
Fogarty International Research Collaborative Awards	2,434,000	2,508,000
Senior International Fellowships	1,101,000	1,101,000
Scholars-in-Residence Program	563,000	563,000
International Research Fellowships	1,581,000	1,581,000
Human Frontier Science Program	500,000	500,000

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Budget Mechanism

	1995 Actuals		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Research projects						
Noncompeting.....	55	\$2,273,000	81	\$2,885,000	80	\$2,956,000
Admin. supplementals.....	(1)	30,000	---	---	---	---
Competing:						
Renewal.....	3	73,000	9	202,000	6	138,000
New.....	47	1,151,000	27	603,000	31	696,000
Subtotal, competing.....	50	1,224,000	36	805,000	37	834,000
Subtotal, res. proj.....	105	3,527,000	117	3,690,000	117	3,790,000
Other Research						
Other research related.....	114	4,609,000	130	5,822,000	126	5,922,000
Subtotal, other research.....	114	4,609,000	130	5,822,000	126	5,922,000
Total, research grants.....	219	8,136,000	247	9,512,000	243	9,712,000
	FTEs		FTEs		FTEs	
Research Management and Support						
Support.....	68	6,514,000	76	6,142,000	76	6,078,000
Total.....	68	14,650,000	76	15,654,000	76	15,790,000

NOTE: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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Budget Authority by Activity

(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
International research activities.....	--	\$7,440	--	\$6,414	--	\$8,136	--	\$9,512	--	\$9,712	--	+\$200
Research management and support.....	75	6,578	68	6,396	68	6,502	76	6,142	76	6,078	--	-64
Total, obligations.....	75	14,018	68	12,810	68	14,638	76	15,654	76	15,790	--	+136
Unobligated balance lapsing.....	13		15		12		--		--		--	
Total, budget authority	75	14,031	68	12,825	68	14,650	76	15,654	76	15,790	--	+136

NOTE: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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Summary of Changes

1996 Estimated budget authority.....	\$15,654,000
1997 Estimated budget authority.....	15,790,000
Net change.....	+136,000

	Current 1996		Change from Base	
	Estimate	Base	Change	Base
	FTEs	Budget Authority	FTEs	Budget Authority
<u>Changes:</u>				
<u>A. Built-in:</u>				
1. Research Management and Support				
a. Within grade increase.....		\$3,568,000		+62,000
b. Annualization of January 1996 Locality and Pay increase.....		3,568,000		+23,000
c. January 1997 pay increase.....		3,568,000		+80,000
d. Increase for FECF and Unemployment Comp.....		26,000		+2,000
e. Payment for centrally furnished services.....		1,107,000		-96,000
f. Service and supply fund increase.....		277,000		+14,000
g. Increased cost of supplies, materials, and other mandatory program expenses.....		1,467,000		+24,000
Subtotal, built-in.....				+109,000
<u>B. Program:</u>				
	No.	Amount	No.	Amount
1. Research Project Grants				
a. Noncompeting.....	81	2,885,000	-1	+71,000
b. Admin supplements.....	—	—	—	—
c. Competing.....	36	805,000	+1	+29,000
	117	3,690,000	—	+100,000
2. Other Research				
a. Other research related.....	130	5,822,000	-4	+100,000
3. Research management and support.....	(FTEs) 76	6,142,000	(FTEs) —	-173,000
Subtotal, program.....				+27,000
Total changes.....				+136,000

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Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	76	76	---
Full-time equivalent of overtime and holiday hours.....	1	1	---
Average ES Salary.....	\$116,689	\$119,402	+\$2,713
Average GM/GS grade.....	9.7	9.8	+0.1
Average GM/GS salary.....	\$35,879	\$37,706	+1,827
Average salary, grades established by act of July 1, 1944 (42 USC 207).	\$78,260	---	-\$78,260
Average salary of ungraded positions..	\$50,000	\$51,163	+\$1,163
Personnel compensation:			
Full-time permanent.....	\$2,673,000	\$2,713,000	+\$40,000
Other than full-time permanent.....	153,000	157,000	+4,000
Other personnel compensation.....	71,000	73,000	+2,000
Special personnel service payments..	<u>52,000</u>	<u>52,000</u>	---
Subtotal personnel compensation....	2,949,000	2,995,000	+46,000
Personnel benefits.....	616,000	633,000	+17,000
Benefits for former personnel.....	3,000	3,000	---
Travel and transportation of persons....	95,000	95,000	---

	1996 Estimate	1997 Estimate	Increase or Decrease
Transportation of things.....	12,000	12,000	—
Rent, communications and utilities.....	275,000	268,000	-7,000
Printing and reproduction.....	67,000	65,000	-2,000
Other services:			
Consulting services.....	35,000	35,000	---
Other Services.....	358,000	358,000	---
Purchases from Govt. Accts.....	1,582,000	1,474,000	-108,000
Operation of GOCO's.....	---	---	---
R&D Contracts.....	---	---	---
Supplies and materials.....	60,000	55,000	-5,000
Equipment.....	90,000	85,000	-5,000
Grants, subsidies, and contributions....	<u>9,512,000</u>	<u>9,712,000</u>	<u>+200,000</u>
Total.....	15,654,000	15,790,000	+136,000

Note: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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Administrative Costs

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	<u>Change</u>
Personnel Compensation:			
Full-time permanent (11.1).....	\$2,673,000	\$2,713,000	+40,000
Other than Full-Time Permanent (11.3).....	153,000	157,000	+4,000
Other Personnel Compensation (11.5).....	71,000	73,000	+2,000
Special Personnel Services Payments (11.8)	52,000	52,000	—
Total Personnel Compensation (11.9).....	<u>2,949,000</u>	<u>2,995,000</u>	<u>+46,000</u>
Civilian Personnel Benefits (12.0).....	616,000	633,000	+17,000
Benefits for former personnel (13.0).....	3,000	3,000	—
Travel (21.0).....	95,000	95,000	—
Transportation of Things (22.0).....	12,000	12,000	—
Rental Payments to Others (23.2).....	—	—	—
Communications, Utilities, and Miscellaneous Charges (23.3).....	275,000	268,000	-7,000
Printing and Reproduction (24.0).....	67,000	65,000	-2,000
Consulting Services (25.1).....	35,000	35,000	—
Other Services (25.2).....	358,000	358,000	—
Purchases from Govt. Accts. (25.3).....	1,466,000	1,358,000	-108,000
Operation of GOCO's (25.4).....	—	—	—
Supplies and Materials (26.0).....	<u>60,000</u>	<u>55,000</u>	<u>-5,000</u>
	<u>5,936,000</u>	<u>5,877,000</u>	<u>-59,000</u>

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Significant Items in House and Senate Appropriations Committee Reports1996 House ReportItem

Infectious Diseases - ...The House in its report 104-209, page 77, stated, "The Committee commends FIC for developing a long range plan which identifies infectious diseases of international origin as a major concern and encourages the Center to continue its efforts in this area. In addition, the Committee recommends FIC consider other transnational factors that contribute to the world's burden of disease, such as biodiversity loss."

Action Taken or to be Taken

The FIC will continue to pursue efforts to deal effectively with infectious diseases. AIDS is an example of a devastating infectious disease that became a world-wide pandemic. Through the FIC's AIDS International Training and Research Program (AITRP) epidemiological and clinical training is being provided to developing country health scientists and professionals in support of future cooperative vaccine and therapeutic trials. AITRP grantees are also addressing emerging and re-emerging infections linked to HIV/AIDS biologically or geographically. Additionally, the International Cooperative Biodiversity Groups (ICBG) Program supports both economic growth and ecological conservation by demonstrating the value of biological resources from which medical products are derived. These two programs serve as models for establishing linkages to meet emerging health problems that are transnational in scope and require international cooperation.

In FY 1996, as directed by the Congress and in cooperation with NIAID, FIC will initiate a grants program for international research and training on new and emerging infectious diseases. Special emphasis will be placed on research and training in those regions of the world that are the potential origin of new epidemics, including the application of new molecular and analytic tools to detect these occurrences. In collaboration with other components of NIH, the CDC, and foreign counterparts, these efforts will become part of a global research sentinel system capable of anticipating and containing future epidemics. The FIC is also planning an international research conference on Ebola and other Filoviruses with NIAID and the Institute of Tropical Medicine, Antwerp, Belgium.

1996 Senate ReportItem

New and emerging infectious diseases -...The Senate in its report 104-145, page 105 and 106, stated, --"The Committee is supportive of plans to provide leadership in the development of research and training programs to mobilize global scientific efforts to meet these challenges through international studies on microbes, hosts, vectors, and environmental and social factors that lead to the emergence of infectious diseases."

Action Taken or to be Taken

In FY 1996, as directed by the Congress and in cooperation with NIAID, FIC will initiate a grants program for international research and training on new and emerging infectious diseases. Special emphasis will be placed on research and training in those regions of the world that are the potential origin of new epidemics, including the application of new molecular and analytic tools to detect these occurrences. In collaboration with other components of NIH, the CDC, and foreign counterparts, these efforts will become part of a global research sentinel system capable of anticipating and containing future epidemics. The FIC is also planning an international research conference on Ebola and other Filoviruses with NIAID and the Institute of Tropical Medicine, Antwerp, Belgium.

Equally insidious health risks are presented by rising concentrations of industrial and chemical pollutants. The FIC's International Training and Research Program in Environmental and Occupational Health, in collaboration with the National Institute of Environmental Health Sciences of the NIH and the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention, supports efforts that address health risks related to environmental change and degradations. The continuing threat of new or newly recognized diseases that may emerge from human encroachment on natural ecosystems and rapid social and demographic change has significant ramifications for global health. The FIC's International Research and Training Program on Population and Health, in collaboration with the National Institute of Child Health Diseases, is designed to create and expand research partnerships between U.S. scientists and counterparts in developing regions of the world on population concerns of mutual priority.

Item

International tuberculosis effort -...The Senate in its report 104-145, page 106, stated, "Elimination of tuberculosis in the United States can only be achieved by controlling the disease in developing countries where more than 90 percent of all the world's cases are presently located...The Committee encourages the Fogarty International Center to combat tuberculosis in developing countries. In this regard, the Committee notes the longstanding work of the International Union Against Tuberculosis and Lung Disease in international tuberculosis control, as well as the resources presently available at the U.S.-

based tuberculosis model centers. Given the relationship between HIV infection and the increased incidence of tuberculosis, this program would seem to be an excellent complement to the already existing and highly successful international AIDS program carried out by the Fogarty International Center."

Action Taken or to be Taken

The FIC's AIDS International Research and Training Program (AITRP) supported expansion of research on tuberculosis and lung disease related to HIV/AIDS, in Tanzania, Cameroon, Malawi, Benin, Mozambique, Nicaragua, Nepal and Vietnam, among other countries. The FIC will continue to work with the International Union Against Tuberculosis and Lung Disease in the above and other efforts dealing with global tuberculosis drug resistance surveillance and other related efforts.

Item

Infectious diseases ---The Senate in its report 104-145, page 106, stated, "The Committee commends the FIC for the work it has done in the area of infectious diseases of international origin. The Committee encourages the Center to continue its efforts in this area, as well as consider other transnational factors that contribute to the world's disease burden."

Action Taken or to be Taken

The FIC will continue to pursue efforts to deal effectively with infectious diseases. AIDS is an example of a devastating infectious disease that became a world-wide pandemic. Through the FIC's AIDS International Training and Research Program (AITRP) epidemiological and clinical training is being provided to developing country health scientists and professionals in support of future cooperative vaccine and therapeutic trials. AITRP grantees are also addressing emerging and re-emerging infections linked to HIV/AIDS biologically or geographically. This program serves as a model for establishing linkages to meet emerging health problems that are transnational in scope and require international cooperation. As previously discussed, the FIC, in cooperation with NIAID, is implementing in FY 1996 a grants program for international research and training in emerging infectious diseases.

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for Advanced Study in the Health Sciences

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Estimate
Research and Investigation.....Section 301	42§241	Indefinite		Indefinite	
International Cooperation.....Section 307	42§242e	Indefinite	\$15,654,000	Indefinite	\$15,790,000
Fogarty International Center.....Title IV, Part E	42§287b	Indefinite		Indefinite	
Total Budget Authority.....			15,654,000		15,790,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Appropriations History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u> 1/
1988	\$11,166,000	\$12,128,000 2/	\$11,166,000	\$15,651,000
1989	11,338,000	16,074,000	16,474,000	15,848,000
1990	10,622,000 3/	15,579,000	15,532,000	15,516,000
1991	16,355,000	18,682,000	17,436,000	17,519,000 4/
1992	19,922,000	19,922,000	19,922,000	19,593,000 5/
1993	20,002,000	19,932,000	19,609,000	19,733,000 6/
1994	19,988,000	22,240,000	19,988,000	21,577,000
1995 7/	13,733,000	15,181,000	13,197,000	14,667,000 8/
Rescission				-21000
1996	15,267,000 7/	25,313,000	14,959,000 7/	25,313,000
1997 7/	15,790,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ Does not include HIV-related funds, which were requested in a consolidated amount under the Office of the Assistant Secretary for Health

4/ Reflects enacted administrative reductions of \$540,000.

5/ Reflects enacted administrative reductions of \$313,000 and rescission of \$16,000.

6/ Reflects enacted administrative reductions of \$268,620.

7/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

8/ Excludes enacted administrative reduction of \$30,000.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	5	6	6
Office of International Science Policy and Analysis.....	7	8	8
Office of Administrative Management and International Services Administrative Management.....	9	9	9
International Services Branch.....	19	21	21
Division of International Training and Research.....	11	13	13
Division of International Relations.....	12	14	14
Division of International Advanced Studies.....	<u>5</u>	<u>5</u>	<u>5</u>
Total FIC.....	68	76	76

Average GS/GM Grade

1992.....	9.0
1993.....	9.6
1994.....	9.6
1995.....	9.7
1996.....	9.7
1997.....	9.8

NOTE: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for the Advanced Study in the Health Sciences

Program Administration
Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Request
ES-4.....	1	1	1
Subtotal.....	1	1	1
Total - ES Salary.....	\$113,180	\$116,689	\$119,402
GS/GM-15.....	7	7	8
GS/GM-14.....	6	8	8
GS/GM-13.....	7	7	7
GS-12.....	7	7	7
GS-11.....	1	1	1
GS-10.....	2	2	2
GS-9.....	10	11	11
GS-8.....	4	4	4
GS-7.....	18	18	18
GS-6.....	1	2	2
GS-5.....	2	3	3
GS-4.....	3	3	3
GS-3.....	0	0	0
GS-2.....	0	0	0
GS-1.....	1	1	1
Subtotal.....	69	74	75

Grades established by Act of
July 1, 1944 (42 U.S.C. 207):

Director Grade.....	1	1	—
Ungraded.....	1	2	2
Total permanent positions.....	70	76	76
Total positions, end of year.....	72	78	78

Total full-time equivalent (FTE)

<u>employment, end of year.....</u>	<u>68</u>	<u>76</u>	<u>76</u>
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Average ES level.....	4.0	4.0	4.0
Average ES salary.....	\$113,180	\$116,689	\$119,402
Average GS/GM grade.....	9.7	9.7	9.8
Average GS/GM salary.....	\$36,379	\$35,879	\$37,706



WEDNESDAY, APRIL 24, 1996.

**NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH
SCIENCES**

WITNESSES

KENNETH OLDEN, M.D., DIRECTOR

CHARLES E. LEASURE, JR., ASSOCIATE DIRECTOR FOR MANAGEMENT

LAURIE JOHNSON, BUDGET OFFICER

**HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF
HEALTH**

**DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET,
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Mr. PORTER. We continue with our hearings for the National Institutes of Health with the National Institute of Environmental Health Sciences. We are delighted to welcome Dr. Kenneth Olden, the director.

Dr. Olden, why don't you introduce the people who are with you and then proceed?

INTRODUCTION OF WITNESSES

Dr. OLDEN. Thank you, Congressman Porter.

On my left is our Budget Officer, Ms. Laurie Johnson; and the Associate Director for Management, Mr. Charles Leasure. Of course you know Dr. Varmus; and that's Mr. Williams.

OPENING STATEMENT

Mr. Chairman and Committee Members, it is always difficult to decide whether to emphasize recent accomplishment or to talk about opportunities for future success. In the arena of success, I could talk about the recent isolation of a human gene that prevents the spread of prostate cancer, and I could discuss the diagnostic and treatment implications of this discovery.

I could talk about the creation of the genetically-engineered mouse that can be used to gain insight into the causes and treatments for colon cancer, arthritis, and inflammatory diseases.

Or I could report the success of a gene therapy experiment in which a human DNA protein was shown to prevent cancer development in mice exposed to various carcinogenic agents.

Nevertheless, I want to take the time allocated to me today to emphasize future opportunities—opportunities that can really change the face of both environmental health sciences and the practice of medicine.

It is appropriate that we have such a discussion of scientific opportunities, because we have entered the modern era of toxicology where scientific opportunities have converged with public health and regulatory need.

The studies that I will briefly describe are important, because nearly all diseases arise from the interplay between genetic inherited alterations and the environment. Thus, a better understanding is needed of the individual functions of critical genes involved in growth and development and the ability of environmental agents to interact with and damage them.

The first important scientific opportunity is to develop animal models of human diseases. These models can be used to investigate the molecular interactions between genes and environmental agents. The absence of such models has been a major impediment in environmental health research.

But new refinements in molecular biology techniques provide unprecedented opportunities for understanding the environmental and genetic basis of many common illnesses and for designing effective prevention and intervention strategies to combat their development.

The creation of animal models of human diseases will allow us to investigate the role of environmental factors in the development of devastating diseases such as cancer, Alzheimer's, Parkinson's, asthma, and osteoporosis, just to name a few.

We have already created a mouse model lacking the estrogen receptor, and we are well on our way to creating a mouse model containing the human breast cancer gene, BRACAI. Both models will be useful in investigating the role of estrogens and environmental agents in the development of breast cancer.

The second important scientific opportunity is to develop a mechanistic understanding of the carcinogenic and toxic action of environmental agents. Insights into molecular mechanisms involved in carcinogenesis and other disease processes are important. They are important in three ways:

First, they can provide a more rational basis for assessing human risk based on data obtained in animals.

Second, they can suggest new laboratory procedures for use in epidemiologic studies to more precisely identify the causes of human illnesses.

Lastly, they can increase understanding of the wide person-to-person variation in risk to disease.

Once the different modes of actions have been deciphered, appropriate risk assessment methodologies can be developed to replace the current approach, which is based on the faulty assumption of a single mechanism of action.

Also, information on mechanisms of action of environmental agents is crucial for development of prevention, detection, and treatment strategies for various diseases.

The third and last important issue that I will discuss is the opportunity to develop new models for use in carcinogenicity testing. Existent measures of carcinogenicity are based largely on rodent bioassays in which mice are fed large amounts of a single chemical. The current rodent bioassay for carcinogenicity testing is too costly, costing \$2 million to \$6 million per chemical, dependent on the route of exposure, and it is too time consuming, taking up to five years to plan, to conduct, to interpret, and to certify.

I am pleased to report that we have developed genetically engineered mice that could become the new standard for carcino-

genicity testing. The genetic alterations were designed to provide results that are faster, with fewer animals and less expense than the current bioassay.

Time has been reduced by four-fold, and animal use and costs have been reduced by as much as three-fold.

Efforts are already underway to obtain validation and regulatory acceptance of the alternative toxicological tests.

In conclusion, environmental health research is at the crossroads of tremendous change. Though the scientific challenges are daunting, rapid advances in a number of fields offer great promise.

As more becomes known, it will be possible to develop regulatory policies based on a better understanding of how environmental agents affect human health. Continued research will eventually provide answers for many of the difficult questions about the link between environment and health.

The President's 1997 request for NIEHS is \$289,114,000. I would be pleased to answer any questions.

[The prepared statement and biography of Dr. Kenneth Olden follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

National Institute of Environmental Health Sciences

Mr. Chairman and Members of the Committee, I too am pleased to appear before you today to discuss the important work of the National Institute of Environmental Health Sciences.

Nearly all diseases are thought to arise from the interplay between inherited genetic alterations and the environment.

Thus, a better understanding is needed of the individual functions of critical genes involved in growth and development and of the ability of environmental agents to interact with and damage them.

To advance our understanding of the role of the environment in the development of human diseases, we have begun major efforts in four areas:

1. Creating animal models of human diseases;
2. Developing more precise methods of carcinogenicity testing;
3. Elucidating how carcinogenic and toxic mechanisms work at the level of the human cell and gene;
4. Translating of laboratory findings into prevention/intervention strategies.

ANIMAL MODELS OF HUMAN DISEASES

For many years, the major impediment in environmental health research was the absence of appropriate animal models to investigate the molecular interactions between genes and environmental agents.

But new refinements in molecular biology techniques provide unprecedented opportunities for understanding the environmental and genetic basis of many common illnesses, and for designing effective prevention and intervention strategies to combat their development.

One of the most remarkable technical advances in biomedical research has been the development of genetically-engineered, or transgenic, mice. Using transgenic mice, we can increase or decrease the expression of specific genes--for example, activation of cancer-causing genes or inactivation of tumor suppressor genes. We can express genes

at a different time, or in a different tissue than normal, and we can determine the function of the modified gene.

Such transgenic mice provide sensitive model systems to study the rate and pattern of disease development, the range of tissues affected, and the interaction of different factors that influence growth and development.

Scientists are, for example, attempting to create a mouse containing the human breast cancer susceptibility gene I (BRCAI). Such a model of human breast cancer will be used to investigate the role of various environmental factors in the development of this devastating disease.

We can also mutate specific genes. These mutations allow us to develop mouse models of human genetic diseases and determine the functions of specific genes by "inactivating" or "knocking-out" a gene function and observing the results in the mouse.

The gene responsible for cystic fibrosis was one of the first to be targeted for knock-out to produce a mouse model of a human disease.

More recently, the gene responsible for the production of the estrogen receptor was "knocked-out" to create a mouse model to study the role of estrogens in the development of breast cancer and other diseases.

Estrogen is an important hormone that directs and controls cell growth and differentiation by binding to estrogen receptors located in tissues throughout the body. Although found in higher amounts in women, estrogens and estrogen receptors are critical for cellular function in both men and women.

Since many breast cancers are responsive to estrogen stimulation, estrogenic exposure is considered an important risk factor in the development of this disease. Part of the difficulty in establishing a possible link between estrogen exposure and breast cancer is the lack of understanding of the role of estrogens in normal growth and development.

Many environmental chemicals mimic estrogens by binding to the estrogen receptor, thus potentially increasing estrogen exposure. While it is generally acknowledged that these chemicals can attach to hormone receptors and cause reproductive and developmental problems in fish and wildlife, we do not know whether such hormone-disrupting activity is a threat to human health. There is very little evidence to date that these chemicals are hazardous at the levels at which they are present in the environment, in food or in human tissue.

Nevertheless, there is cause for concern because of the widespread distribution and vast number of agents, present in the environment, that behave as endocrine disrupters. Another reason for concern is because the endocrine system plays such a critical role in growth and regulation of bodily functions, anything that would disturb these pathways has the potential to adversely effect numerous organ systems.

IMPROVED RISK ASSESSMENT THROUGH THE USE OF NEW MODELS AND METHODOLOGIES

Though the situation is improving, the dilemma facing environmental and regulatory scientists is lack of animal models that completely duplicate the toxic or carcinogenic response of humans. Most of the scientific data used to determine the toxic or carcinogenic properties of environmental agents are derived from experimental animals, typically rodents. Such studies have resulted in a great deal of dissatisfaction, mostly due to unresolved uncertainties and the time and costs required for the conduct of the conventional two-year rodent bioassay.

Assessment of dose-response relationships and relevance of the experimental model are often the most difficult and controversial issues in risk assessment. Data in experimental animals are usually obtained with relatively high doses of exposure because of limited resources and the need to minimize the numbers of animals used. This requires use of methods to extrapolate health effects to exposure levels much lower than those for which experimental data are available. Depending on the methods used, risk estimates may vary by several orders of magnitude.

To address this important issue, greater emphasis has been placed on developing a mechanistic understanding of disease causation for use in extrapolating from rodents to humans, and on developing quicker and cheaper alternatives to the current two-year rodent bioassay to enable more efficient use of resources. Mechanistic data is now routinely generated during the performance and evaluation of the results of the rodent bioassay. Also, new transgenic mice are being evaluated for their effectiveness in producing reliable and relevant carcinogenic information in a shorter time frame--six months versus two years--using fewer animals.

Preliminary results with the transgenic mice have been very promising. Of the approximately 40 chemicals screened to date, test outcomes are comparable to those reported for the traditional two-year rodent bioassay. Partnerships have been developed involving industry, the Environmental Protection Agency, and the Food and Drug Administration to complete validation of transgenic models within two to three years. If validated, the new transgenic models could reduce our dependency on the costly and time-consuming two-year rodent bioassay and would allow for screening of dozens of chemicals annually. Further, the results would be more relevant for the assessment of risk to human health because the tests can be performed with low dose exposures. We estimate that four chemicals can be screened in the new system for the price of a single chemical in the two-year rodent bioassay. Additionally, representatives of the pharmaceutical industry have indicated that shortening the carcinogenicity test from 24 months to six months will result in a net benefit of hundreds of millions of dollars for every "so-called" typical drug introduced into the marketplace. Thus, the potential impact of these new models on carcinogenicity testing, human risk assessment, and on the Nation's economy is substantial.

STORIES OF DISCOVERY

Prostate Cancer Metastasis Gene: For men, prostate cancer is arguably their greatest cancer fear. Not only does it account for one in every four cancers diagnosed in American men, but it can spread--metastasize--beyond the prostate, killing 40,000 men annually. Although only 25% of these cancers are the lethal variety, physicians have no way of determining which prostate cancers can be ignored and which must be surgically removed. This dilemma is further complicated by the fact that prostate cancer surgery is not a benign procedure; it requires a lengthy recovery time and frequently renders a man incontinent or impotent. A biological marker that identifies which patients are truly at risk of the cancer spreading beyond the prostate, and thus meriting surgery, would prevent unnecessary surgeries among men with non-metastatic prostate cancers. NIEHS intramural researchers, working with colleagues at John Hopkins University, have isolated the first such marker. This gene, KAI1, was shown to suppress the spread of prostate cancers in experimental animals and it appears to be lost in metastatic human prostate cancers. Its discovery will initially lead to better identification of patients requiring prostate cancer surgery. Its identification also enhances our ability to develop therapeutic strategies to more effectively treat this devastating disease. Ultimately, studies on this gene will help us identify the environmental components leading to prostate cancer development, thus enabling us to prevent its development in the first place.

Lead Exposure, Its Link to Criminal Behavior, and Its Treatment: NIEHS-supported researchers have shown that the developing fetus and young child are particularly susceptible to lead and that their brain is the most vulnerable target. Further research, published in 1990, revealed that even at exposures previously thought to be safe, young children suffer from measurable decreases in IQ scores and exhibit anti-social and delinquent behavior and now a new study on a cohort of young boys in Pittsburgh's inner city confirms that above-normal lead values in bone are associated with more aggressive and delinquent behavior, such as bullying, vandalism, theft, fighting, and setting fires. These behaviors foreshadow the development of more serious problems as these boys become adults, including adult criminality, alcoholism, and domestic abuse. It is notable that inner city environments, which are known to have high crime rates, also suffer from high levels of environmental lead. These studies suggest a need for enhanced lead prevention programs as part of a strategy to improve public safety.

Molecular Prevention/Intervention of Environmentally Induced Cancers: DNA repair proteins are one of the body's most important defenses against environmental cancer-causing agents--carcinogens. When environmental or other factors have damaged a gene, these repair proteins can often make corrections like "spell check" on a computer. NIEHS extramural and intramural scientists are studying this vital protective mechanism. This research has tremendous potential in being used to develop molecular intervention techniques, as was recently demonstrated by NIEHS extramural researchers. These scientists developed a transgenic mouse that can be made to overexpress a specific human DNA repair gene, *O⁶-alkylguanine-DNA alkyltransferase*. Using this transgenic model, investigators can study the ability of a human DNA repair

protein to prevent tumor induction by environmental carcinogens. In one set of experiments, mice overexpressing this human gene in the thymus had a dramatically reduced incidence of lymphoma/leukemia following exposure to methylnitrosourea. Similarly, introduction of the DNA repair gene into cells of the colon, lung and liver prevented tumor formation when animals were exposed to carcinogens known to produce tumors in these organs. These results have obvious important implications for cancer prevention.

CONCLUSION

In conclusion, there is an urgent need to improve the process of hazard identification. Not just so that more chemicals can be evaluated, but also to achieve a better understanding of risk. Uncertainties in risk assessment divide our country and polarize groups and organizations whose cooperation is needed to protect human health and promote our economy. By understanding the genetic and environmental basis of human diseases, billions of dollars could be saved with respect to expenditures associated with health care and regulatory compliance.

The capabilities of the technologies that I have described today are as different from those that we are presently using to make risk assessment decisions as a Boeing 747 aircraft is from the plane flown at Kitty Hawk by the Wright Brothers 93 years ago. The Institute is in a unique position to take advantage of these technologies and those that will inevitably arise in the future.

The budget request for FY 1997 is \$289,114,000. I would be pleased to answer any questions.

KENNETH OLDEN, Ph.D.

Director, National Institute of Environmental Health Sciences (NIEHS) and Director, National Toxicology Program (NTP)

July 22, 1938. Parrottsville, Tennessee

Education: B.S., Knoxville College, 1960; M.S., University of Michigan, 1964; Ph.D., Temple University, 1970 (research done in absentia at the University of Rochester).

Professional History: 1964-65, Research Assistant, Department of Biological Chemistry, Columbia University. 1970-74, Research Fellow and Instructor of Physiology, Harvard University Medical School. 1974-77, Senior Staff Fellow, Division of Cancer Biology and Diagnosis, National Cancer Institute. 1977-78, Expert (Biochemistry) Division of Cancer Biology and Diagnosis, National Cancer Institute. 1978-79, Research Biologist, Division of Cancer Biology and Diagnosis, National Cancer Institute. 1979-82, Associate Director for Research, Howard University Cancer Center, and Associate Professor of Oncology, Howard University Medical School. 1982-84, Associate Director for Research and Deputy Director, Howard University Cancer Center, and Associate Professor of Oncology, Howard University Medical School. 1984-85, Associate Director for Basic Research and Deputy Director, Howard University Cancer Center, and Professor of Oncology, Howard University Medical School. 1985-91, Director of the Howard University Cancer Center and Professor and Chairman of the Department of Oncology, Howard University Medical School. 1991-present, Director, NIEHS and NTP.

Professional Organizations: American Society for Cell Biology; American Society of Biological Chemistry; American Association of Cancer Research; Society for Biological Response Modifiers; Metastasis Research Society.

Honors, Awards: Porter Development Postdoctoral Fellow, 1970. NIH Postdoctoral Fellow, 1970-73. Macy Faculty Fellow, 1973-74. Citation Classic, Current Contents, Life Sciences, 1980. Member, Division of Cancer Biology and Diagnosis Board of Scientific Counselors, National Cancer Institute, 1981-85. Member, Public Policy Committee of the American Society for Cell Biology, 1984. Co-Chairman, Mid-Atlantic Region of National Black Leadership Initiative on Cancer, 1987-89. Member, Board of Directors, Association of American Cancer Institutes, 1987-90. Member, Division of Cancer Treatment Board of Scientific Counselors, National Cancer Institute, NIH, since 1988. Selected as "One of sixteen historical and contemporary role models" for the Museum of Science and Industry exhibit on Black Achievers in Science, Museum of Science and Industry, Chicago, IL, 1988. Member, Board of Directors of Association of Minority Health Professions Schools, 1988-present. Member and Co-Chairman of National Advisory Committee on Socio-Economically Disadvantaged of The American Cancer Society, 1988. Member, Advisory Panel Council for Cell Biology, National Science Foundation, 1989-90. Presidential appointment to membership on the National Cancer Advisory Board, 1991. Associate Editor of Cancer Research, The Journal of the National Cancer Institute, Cell Regulation, and Environmental Health Perspectives. Elected to membership in the Institute of Medicine in 1994.

ENDOCRINE DISRUPTERS

Mr. PORTER. Dr. Olden, thank you for your oral testimony.

Let me begin with a question that came from public witness testimony this year, from one of the authors of the book, "Our Stolen Future: Are we Threatening our Fertility, Intelligence, and Survival?" I know the book has created some controversy in the scientific community. I wonder if you would comment on the book's thesis.

Dr. Varmus, you might want to comment, as well.

Dr. OLDEN. Thank you, Mr. Chairman. The book by Dr. Theo Colburn raises several important issues. She bases her thesis on the fact that we have demonstrated that environmental agents with estrogenic activity can cause serious health problems in fish and wildlife.

For example, reproductive success and mating behavior are altered. There are abnormalities in reproductive organs' formation, and embryonic development is impaired. So there is substantial evidence in wildlife that what she describes as "hormone disrupters" do, in fact, impair normal development and reproductive function.

However, she makes an association between the findings in wildlife and certain trends that are occurring in humans. For example, increases in all the cancers that might have a relationship to endocrine action—for example, breast cancer, prostate cancer, ovarian cancer, testicular cancer. She talks about increases in reproductive dysfunctions. There is an increase in the number of undescended testes in males. She also describes decreases in sperm count. There have been at least two to three reports that demonstrate or claim that sperm counts have decreased by 50 percent over the last 20 years.

[CLERK'S NOTE: Subsequent to the hearing NIEHS changed this number to "50 years" for the record.]

However, the problems with this association are at least three: for one, we are exposed to estrogens in the environment from plant sources at much higher levels. In other words, our exposure to plant estrogens would dwarf our exposure to synthetic chemical agents.

Another one is pharmaceuticals. There are many pharmaceuticals with estrogen or that have hormone disrupting activity that far exceeds any exposure to environmental agents.

Finally, individual variability in estrogen level far exceeds anything that one could possibly obtain from an environmental exposure.

Now, she has raised important issues that are cause for concern. I think her book does point out the possibility that environmental agents that disrupt hormones could be important.

For example, there are a number of agents in our environment—in other words, there is a wide distribution of agents that, in fact, disrupt hormone mechanisms, so from that point of view we should be very concerned. These agents also are persistent. They have very long half-lives, so they can accumulate in the food chain.

Finally, any agent that would disrupt a hormone action would be potentially serious, because hormones regulate homeostasis, they

regulate coordination between various organ systems, and hormones control growth and development and differentiation.

We know very little about what the effect of a hormone exposure might be at the inappropriate time during development.

So yes, there are causes for concerns based on the information that we know from wildlife, but there is absolutely no evidence that environmental agents with estrogenic or hormone disrupting activity at the level to which humans are exposed are causing any disease.

Now, the one that's been looked at for many, many years has been DES. DES has been investigated—in my own institute—and, using high doses of DES, one can demonstrate all the effects that we have seen in wildlife in mice.

There is an additional study using high-dose exposures of estrogen during embryonic development of a rat. In that case the rat subsequently developed prostate cancer.

So there is evidence at high-dose exposures, but, the fact is that we consume a diet where these endocrine disrupters would dwarf anything that we would take up from the environment from industrial or synthetic or manmade chemicals.

Mr. PORTER. Dr. Varmus, would you like to comment on it?

Dr. VARMUS. I certainly would echo some of the skepticism that Dr. Olden has raised. The book, which I have not read completely, is heavier on polemic than on balanced evaluation of the data. I do think the issues are significant. I'm looking forward to a National Research Council study that's in progress, addressing many of the same issues, and I hope will achieve a thorough evaluation of what is, in many cases, a set of conflicting data, particularly in the area of sperm counts and fertility.

There has been a recent conference on the issue of possible effects of hormone disrupters on fertility and sperm counts, coming to what I think to be somewhat different conclusions—much less clear evidence that there has been an effect. Obviously the fertility of the human race warrants surveillance. I have no argument with the idea that these issues should be paid attention to.

Mr. PORTER. How soon would that report be available?

Dr. VARMUS. Well, I've been discussing this issue with my colleague, Bruce Alberts, the president of the National Academy of Sciences, trying to get the report through as quickly as possible. I think it has been written. But it will be subjected to the stringent review process that all Academy reports are subjected to. I am urging him forward with this, especially in view of publication of the book.

Dr. OLDEN. Mr. Porter, I think the institute anticipated the needs in this area because we initiated research several years ago and, in fact, we're supporting at the present time about \$7 million worth of research in this area, and as of next week, we will increase that support to \$10 million by funding eight new grants.

I know the Environmental Protection Agency also had workshops.

So I think the needs are important, but I think we're on top of it, and I think we have in place the research activities to address this potentially important public health issue.

Mr. PORTER. Mrs. Lowey?

Mrs. LOWEY. Mr. Chairman, I just would like to say that I, too, met with Dr. Colburn, and I, too, didn't complete the book, but I am equally concerned and look forward to the research that's being done.

In fact, as we drink this water from this pitcher, the water that I believe, Mr. Chairman, has been proven to not be up to standards, and therefore most of our offices have gotten water coolers, I wonder how seriously we take this issue in the House.

I was just talking about the water which we're drinking here, which has been proven to have some problems with it.

I just wonder, in fact, what kind of work is being done, not only following up on Dr. Colburn's premise, but overall on the water supply and the connections between certain diseases. In fact, I even wonder whether we've done an adequate enough job—maybe this is a question for the FDA—on providing strict enough standards for all the bottled water that is making so much money around this country. I gather that the criteria for selling this water as spring water, or whatever, is not very clear at all.

I share the concerns of Mr. Porter, our chairman, and I look forward to the research that is being done.

Dr. OLDEN. Well, as it relates to the water in this pitcher, there are reports that plastic does leach out estrogen, but the estrogenic activity that is discovered is very, very weak, and it is still uncertain as to whether this level of exposure causes any impairment to human health.

There is no doubt that high levels of exposures do cause disabilities and will cause health problems. This is certainly in animal studies, both rat and mice, and, in fact, in humans, because that's how DES was first discovered—in humans that were exposed in utero. Serious consequences such as clear cell carcinoma of the vaginal tract, as well as reproductive abnormalities in males occurred later on in life.

So it is documented at high levels of exposure, but the levels of exposure that might be in our water supply, there is just really very little evidence to substantiate that.

Mrs. LOWEY. Actually, I was referring to all the other things in our water.

Dr. OLDEN. I know you were.

Mrs. LOWEY. But I thank you very much, and I look forward to seeing the results of this research, and I apologize for coming in late.

RESEARCH TRIANGLE PARK LOCATION

Mr. PORTER. Dr. Olden, some members of the subcommittee may be unaware that your institute is located in Research Triangle, North Carolina. Could you review for the record the history behind your location in North Carolina and tell us what benefits and disadvantages you believe it offers?

Dr. OLDEN. Well, I think there are a number of benefits in one sense. It is the center for environmental health science research. The three major environmental health research agencies in this nation are located in Research Triangle Park—NIEHS, the Health Effects Research Laboratory of the Environmental Protection Agency,

and the Chemical Industry Institute of Toxicology. So the three of us can create partnerships. We can collaborate. We can talk.

I think these kind of interactions between NIEHS and EPA are crucial, and I think interactions with industry are crucial, so I think the kind of partnerships that are desired are pretty much in place as a consequence of our proximity in the same area.

It was located there because I understand there was a law in place at the time that our institute was created in 1969 that said any Federal agency created must be 50 miles outside the District of Columbia. That puts it outside of Bethesda. And once that's beyond Bethesda, then it could be in any State, and I guess, after that, it was simply a matter of deciding which State it should be located in. The Research Triangle Park was trying to develop in those days, and President Lyndon Johnson agreed with the governor of North Carolina, Mr. Luther Hodges, that he would put the center there.

But now there are many other Government agencies, and, in fact, the Environmental Protection Agency will be located on the same campus as we are, and we can soon share a lot of resources, which will reduce our overhead.

Now, a disadvantage, of course, is that our research and management support and our overhead is a bit higher than for institutes that are located in the Bethesda campus because they can share. We share some things with Bethesda, obviously, but obviously the sharing has to be somewhat reduced. So our overhead is a bit higher.

But other than that, we interact very well with the Bethesda campus. I'm up here every week, so we have a lot of collaboration with the Institutes of NIH, so the relationship is very good. And, I think, from a scientific point of view, there are no—I'm not aware of any—drawbacks from being located in North Carolina. We have to work at it.

Dr. VARMUS. Our only problem, Mr. Chairman, is that we're very proud of the institute, and it's sometimes not known that NIEHS is actually part of NIH.

Mr. PORTER. How much time do you spend in North Carolina, Dr. Varmus?

Dr. VARMUS. I have been, but——

Dr. OLDEN. Not enough, Mr. Porter.

Mr. PORTER. Not enough.

Dr. VARMUS. We do effective collaborations there, but I rely on Dr. Olden to do the traveling.

Mr. PORTER. Well, since we had that law in 1969, the law has been changed, and Senator Byrd has decided that all new Federal agencies have to be in West Virginia. [Laughter.]

CONTRACT MECHANISM

Mr. PORTER. Dr. Olden, your institute uses the contract mechanism more heavily than some other institutes. In a year in which the NIH budget focuses on research project grants as a top priority, has your institute been disadvantaged? Could you shift some of your contracts into the Research Project Grant pool, or does your work require the greater central direction of contracts?

Dr. OLDEN. We had already begun to move a lot of the contracts into the RPG line anyway, Mr. Porter. We felt that we could get better research by using a peer review investigator initiated process, so we had already begun the trend of downsizing our contracts and investing in research grants.

For example, we now have at least two sets of National Toxicology Program grants. We're looking at the health effects of pesticides, that was a Request for Applications that we announced, and in response to the RFA we have funded a number of grants looking at the health effects of pesticides to get at the issue that you asked me about about endocrine disrupters. We are focusing on early development, in utero and shortly after birth, in animals. And we are also looking at the health effects of pure estrogens on early development. Again, that work has been supported through a grant mechanism.

This year, with the 1996 appropriation, we increased our RPG line by almost 10 percent. In contrast, our contracts line went up only about 4 percent.

[CLERK'S NOTE:—Subsequent to the hearing NIEHS corrected this figure to 7 percent for the record.]

So it creates no problem for us whatsoever, because I think we are simply getting a better product by using the RPG mechanism than we were using the contract mechanism.

Mr. PORTER. Mrs. Lowey.

ASTHMA

Mrs. LOWEY. Thank you, Mr. Chairman.

There is an increase in asthma and other respiratory illnesses in children. What is your institute doing to examine the link between the environment and these illnesses? And have you found any means of decreasing these illnesses? In fact, I believe it's not just children. There seems to be a great increase in asthma, according to recent reports.

Dr. OLDEN. Yes. Asthma has gone up several-fold in recent years, and yes, we have started a number of new initiatives to address asthma. We're doing these studies mainly in collaboration with the Heart, Lung, and Blood and Allergy and Infectious Diseases Institutes.

For example, with Allergy and Infectious Diseases, we're supporting the inner-city asthma project, and what we're doing in that project is to see if, by remediation of indoor allergens—dust mites, cockroaches—we can reduce the incidence of asthma among inner-city kids.

We are also, with Heart, Lung, and Blood, looking at trying to identify the outdoor pollutants that cause asthma, focusing on ozone and oxides and nitrogen and sulphur.

We are focusing on the two possible causes, but it's not really clear which is going to be the primary environmental trigger, and we're focusing, in addition, on the interaction between outdoor pollutants and indoor allergens.

Those are the three studies that we are supporting. We are also looking at basic, fundamental mechanisms, inflammatory processes. That's asthma.

So the four kinds of studies are those, and, except for the basic science effort, all of the others are done in collaboration with Heart, Lung, and Blood and Allergy and Infectious Diseases.

Mrs. LOWEY. While the chairman's away, I could follow up a bit. Have these increases in asthma been regional, or are they in specific parts of the country, or is it across the country that you've seen it?

Dr. OLDEN. It's across the country; however, it's more in inner cities and among minority youths—blacks, Latino. The Hispanic community is where the largest increases are occurring, and increases as much as four- to five-fold have happened in recent years.

In the first phase of our study with the inner-city asthma project, it looks like indoor allergens—certainly we can control the onset of crisis by remediating the indoor environment. And smoking indoors on the part of parents is also an important factor that will exacerbate the indoor allergen exposure.

So it is across the U.S., it doesn't appear to be regional, but ozone and oxides are probably fairly comparable in most major metropolitan areas.

Mrs. LOWEY. In fact, you mentioned sulphides—I was very much involved several years ago in an issue with the FDA involving sulfides and, as you know, the percentage of sulphides in foods ranges widely. I've never felt they've been regulated as closely as they possibly should. Are you doing any work on that—the connections between the percentage of sulphide in shrimp, for example, and wines and frozen potatoes?

Dr. OLDEN. No. I'm not aware of any research in that area. Let me say, I should add that on the air pollution in the United States—it is called "smog," in California—we're comparing air pollution in the United States mainland versus the State of Hawaii where there is an active volcano that emits the same kind of gases.

We believe that the emissions in the U.S. mainland are different from automobiles and from smokestacks, and we think the particles are also contaminated with petrochemical carcinogenic and other agents. Whereas in the State of Hawaii on the big island it's probably pure, and it will give us a good chance to compare and see if it's really the oxides or air particles, ozone, or is it some other pollutant, or some combination of all of those.

LEAD

Mrs. LOWEY. I'm not sure if I have time to ask my question about lead, Mr. Chairman.

In 1990, your institute published an important finding related to lead in children. Has your institute continued its research on the impact of lead? And what are your most recent findings? And have your findings been disseminated among the public health community?

Given your Institute's concrete findings, has there been any decrease in lead exposure? What has been the impact of this information?

Dr. OLDEN. We have, indeed, continued our research on lead, and there have been two major reports just this year—one last week and one, I think, about two months prior to that.

Dr. Herbert Needleman, the person that made most of the significant discoveries with respect to low-level leads, reported about two months ago that bone lead, not just blood lead, causes children to develop a kind of irrational, anti-social, criminal behavior. In fact, he went as far as to suggest that maybe some of the criminal behavior that we see in inner cities is, in fact, due to these high bone lead levels.

Just last week Howard Hu of Harvard published a report where he demonstrated that bone lead was responsible for kidney dysfunction, kidney diseases, and that high blood lead was responsible for hypertension. Considering that, in the inner city, and particularly among African-Americans, a major public health problem is hypertension and kidney diseases, these findings may account for the disproportionate disparity that is observed in inner city environments among African-Americans.

So there have been those two, I think, important reports over the past two months.

Mrs. LOWEY. I have to say, Mr. Chairman, as you know, I mentioned before that I'm concerned about the water and the fact that we found lead in the water here, and I wonder if these results—these erratic behaviors, etc., can be attributed to lead's impact on adults, as well. You don't have to answer that. [Laughter.]

Dr. OLDEN. I should point out, I didn't state that the Howard Hu study was in adult males, so this is the very first study that demonstrates the health effects of high lead in adults. All the other studies, the Needleman studies, are done with children, usually between ages zero to six, although his recent study was with high school children in the city of Pittsburgh where he demonstrated an association between blood and bone lead and criminal behavior. But the Harvard study was with adults.

Mrs. LOWEY. I just want to conclude by saying—I won't carry it as far as calling it criminal behavior, but perhaps the erratic behavior of some Members of Congress can be attributed to the water we drink.

Thank you very much, Dr. Olden.

Mr. PORTER. She doesn't mean members of the subcommittee.

Mrs. LOWEY. Of course not. Not from where you stand over.

GENETICS VERSUS ENVIRONMENTAL EXPOSURE

Mr. PORTER. Your testimony describes the development of DNA repair proteins that could one day protect genes against environmental damage.

Dr. OLDEN. Yes.

Mr. PORTER. If genes can ultimately be adjusted to prevent environmental impacts, is genetics research more important than research that attempts to define the impacts of environmental exposures?

Dr. OLDEN. I think, Mr. Chairman, both are equally important. I think if we made an investment just to understand the genetic basis of human disease and dysfunctions, it would be short-sighted, inappropriate to really do the job.

I think it's important to understand the genetic basis of human diseases. I think it's also important to understand the environ-

mental basis. But, more importantly, it's important to understand how the two interact.

I think in most cases—in fact, the reports that are just coming out of the American Association of Cancer Research meeting this year, almost all the presenters, when they are talking about the impact of genes on breast cancer, ovarian cancer, prostate cancer, are very clear to point out that it is likely ultimately an interaction between the two.

Certainly one can inherit a predisposition for breast cancer, prostate cancer, colon cancer, asthma, but in most cases illness is the consequence of gene/environment interaction. If we take asthma, because it is a very clear example, just because one inherits a predisposition to be asthmatic does not mean that one is necessarily asthmatic and is always in crisis. It requires an environmental trigger.

I think that's going to be the case for most diseases, although there may be exceptions both ways. There may be exceptions where genes are the major contributing factor, and there may be exceptions where the environment is the major contributing factor. But I think, on balance, it's going to be an interaction between the two, and if we want to prevent human diseases, illness, I think we have to understand both.

And I must say we've, I believe, convinced Dr. Varmus, during his tenure, and we've had very good support, and I think he, even though he's a genetic person, I think he fully appreciates the importance of the environment in the public health mission of the NIH and the Department.

Dr. VARMUS. I'd point out that most of my work is addressed to somatic mutations, which, of course, occur during the lifetime of an individual, in part due to encounters with environmental factors.

Dr. OLDEN. Yes. Exposure. Right.

REORGANIZATION

Mr. PORTER. As we heard this morning, Dr. Klausner is reorganizing the Cancer Institute very substantially. Has this triggered any change in the way your institute designs its research portfolio or interacts with NCI?

Dr. OLDEN. Mr. Porter, I could say that maybe the changes that we initiated in our institute four years ago triggered the changes that Dr. Klausner initiated in NCI. [Laughter.]

When I became director four years ago, we did much the same thing at our institute that Dr. Klausner has done at the NCI. We had three divisions, three intramural divisions, which we merged into one, and we merged them into one for the same reason, and that is we felt that there needed to be better accountability for the resources. We felt that there was probably duplication. There was lack of adequate communication. And we felt that the scientific product was not as good as it could be if we focused our resources and reorganized, and so we did.

We made a lot of changes. We've had almost every single program of the institute peer reviewed. We, on our own, just initiated an overall review of our institute by a committee, and we put it together and got Dr. Varmus' blessings on the composition of the committee.

I commissioned a review of the institute comparable to the Bishop Calabresi report for the NCI.

I think, Mr. Porter, good leadership requires exactly what Dr. Klausner has done, but it is not unique to NCI, and clearly our model is not something that we're still going through. It's finished. In other words, our reorganization is finished, it's in place, and it's paying dividends.

OVER-THE-COUNTER DRUGS

Mr. PORTER. Your budget justification indicates that over-the-counter drugs, which we assume to be safe, may contain harmful ingredients that were developed prior to regulatory testing requirements. The document cites, as one example, an over-the-counter laxative which contained a carcinogenic substance. Do you think this circumstance is an isolated incident, or does it reflect a potentially significant public safety problem?

INTERACTION WITH NCI

Dr. OLDEN. Before I answer that one, Mr. Porter, can I just go back to the previous question?

Mr. PORTER. Sure.

Dr. OLDEN. The reorganization of the National Cancer Institute also greatly improved the interactions between our two institutes. That was one area, after we reorganized our own institute, after we thought we had the right people, the right programs, the right organization, there was still one area of dissatisfaction on my part, and that was the level of interactions with the National Cancer Institute, because the primary focus of the research program of NIEHS is cancer.

I can say, since Dr. Klausner has been there, that the interactions have increased dramatically. We have a lot of plans to do things together, and I think, certainly for the first time during my tenure at the institute, I can assure you that we are going to jointly address the genetic and environmental bases of cancer, which I think is very important.

Mr. PORTER. Go ahead.

PHENOLPHTHALEIN

Dr. OLDEN. Your question about phenolphthalein—well, we conducted a study of phenolphthalein, which is the active ingredient in probably most laxatives. We tested it as a single agent the way we typically do in two species and in both sexes. We tested in mice and rats and in both males and females.

We tested it at three different doses. All the doses are higher than the kind of exposures that one would get if you use laxatives as they are prescribed. What we discovered was cancers in both species, both mice and rats. We discovered cancers in multiple organs. And we discovered cancers developed in both sexes.

Now, that's the strongest evidence that we ever get for a chemical agent being carcinogenic, so that is absolutely the strongest.

We reported that information to the Food and Drug Administration, and, in fact, FDA is represented on our advisory committee, so they were there when we reported the results to the public.

They are aware of our findings; however, the issue is—and I think I agree with the decision at FDA—that if laxatives are used as prescribed, phenolphthalein may not be causing cancer in humans. Although we don't know absolutely unequivocally. We just started additional studies to clarify this issue. But the FDA alerted all the physicians of our findings. They sent out an alert. But they haven't changed the legislation or regulation on laxatives, because I guess it is their view that at the level at which people would be exposed if used properly, it does not pose a threat to humans.

I think that's an appropriate decision based on the science.

Mr. PORTER. Dr. Olden, I have additional questions for the record, several of which deal with the subject of nano-fabrication, that I'm very concerned about and interested in. We would ask that you answer those questions as promptly as possible.

Mr. PORTER. Let me thank you for the fine job that you're doing at NIEHS and for your good testimony today. Thank you very much, Dr. Olden.

Dr. OLDEN. Thank you very much.

[The following questions were submitted to be answered for the record:]

TRANSGENIC MICE

Mr. Porter: In your testimony, you indicated that the use of transgenic mice was quicker and cheaper than the traditional two-year rodent bioassays for testing the carcinogenicity of chemicals. With current resources, how many chemicals can you test a year with the use of transgenic mice as compared to traditional methods?

Dr. Olden: In our experience, to evaluate one chemical in one transgenic mouse model costs between 10 and 20% of the cost of a traditional 2-year bioassay using one strain of mouse and one strain of rat. We project starting 13 chemicals in traditional 2-year studies by the conclusion of FY 1996, and 12 to 19 studies in FY 1997. If these studies were done using only one transgenic mouse model, approximately 65 to 130 chemical studies could have been started in FY 1996, and a similar number in FY 1997, although it is not yet clear whether one or several transgenic mouse models will be needed to provide data sufficient to satisfy the needs of the scientific/regulatory community.

PARTNERSHIPS WITH INDUSTRY

Mr. Porter: I would think that a number of industries would benefit greatly from the toxicological testing that you do, either in product development or worker safety programs. Have you pursued the possibility of co-funding some of your studies with the industrial partners who benefit from them?

Dr. Olden: The National Toxicology Program (NTP) is an important component of a coordinated government/academic and private industry effort in chemical toxicity evaluations. Although co-funding studies by combining monies has not been common, cost sharing has occurred through other means and informal partnerships have been a normal course of business.

Recently, the NTP has initiated efforts to establish more formal partnerships. We are focusing on three projects which are being developed cooperatively with interested industry, academic and other groups. One involves the worldwide coordination of the evaluation of several different transgenic mouse models for carcinogen identification; a second involves the creation of an entity which would carry out an unbiased scientific review of agents or substances thought to pose a threat to human reproduction and development, and the third promotes the development and regulatory agency acceptance of toxicology test methods that reduce the numbers of animals required, and provide approaches for generating more accurate, faster and less expensive toxicological evaluations. All three efforts will, if successful, benefit the toxicology/regulatory community as well as affected industries.

ELECTROMAGNETIC FIELDS

Mr. Porter: In an article in Science magazine last September, the link between electromagnetic fields and cancer was disputed. What is your view of the state of the science in this field?

Dr. Olden: The potential human health hazard of exposures to electric and magnetic fields associated with the generation, transport and use of electricity is controversial because many of the reported research findings cannot be replicated. NIEHS was named the lead agency for health research on the potential hazards of exposures to these fields as indicated in Section 2118 of the 1992 Energy Policy Act. In collaboration with the Department of Energy, NIEHS has begun an aggressive research program to determine what biological effects can be replicated and what association with adverse health effects may exist. We currently have 27 Extramural investigators funded by NIEHS with the main focus on cancer. We have also identified several intramural investigators who are examining critical aspects linking magnetic field exposures to cancer. We also have, in collaboration with DOE and with FDA and NIOSH, established regional EMF exposure facilities to replicate the critical studies suggesting a link between magnetic fields and cancer processes. NIEHS, through the National Toxicology Program also has a large rodent study where rats and mice are exposed to up to 10 Gauss--nearly 5,000 times residential exposure--for two years. The NIEHS effort will reduce this uncertainty about electromagnetic fields and cancer as results from the Energy Policy Act studies are reported.

SYNTHETIC CHEMICALS

Mr. Porter: Is there now sufficiently reliable information to set legal limits for synthetic chemicals released into the environment and to monitor those chemicals cost-efficiently? Is further research necessary to develop methods for standardizing and monitoring trace toxins, as well as disease-causing bacterial and viral agents, in the environment?

Dr. Olden: We believe that there is insufficient information available to set legal limits for many of the synthetic chemicals released into the environment. This is due more to an insufficient database on human and animal health effects information, than to an inability to detect the presence of chemicals in the environment. Although analytical techniques for monitoring chemical contaminants in the environment are quite sensitive, improvements could be made in their ease of use and in their costs. Additionally, methods are needed to detect interactions of environmental chemicals with cellular constituents in humans exposed to those chemicals. Such methods would enhance our ability to determine which exposure situations in the environment or workplace pose health risks.

NANOFABRICATION

Mr. Porter: Does the incorporation of cell and molecular biology into the techniques of nanofabrication - which is the synthetic preparation of material and devices with structural dimensions of approximately one-millionth of an inch -- and molecular self-assembly hold promise for improving the detection, prevention, and remediation of environmentally related illness?

Dr. Olden: The NIEHS is keenly interested in developing new means for the detection and prevention of environmentally related illness. As you point out, nanofabrication is a technology that holds promise in a number of areas that potentially relate to biomedical sciences and environmental health. The Institute is actively interested in pursuing these technologies especially as they have the potential of providing cost-effective tools that will allow for detection of minute quantities of environmental agents.

Mr. Porter: Given that some synthetic chemicals are present and may be toxic in extremely small concentrations, is it appropriate for NIEHS to support the development and application of new analytic techniques, based on nanofabrication and molecular assembly, that can produce sensors capable of monitoring and detecting minute quantities of such chemicals in the environment?

Dr. Olden: Yes, the NIEHS is very interested in this new technology as it relates to the effect of chemicals that are highly toxic in extremely small concentrations. As a component of the mandate under the Superfund Hazardous Substances Basic Research and Training Program, the NIEHS is conducting research on environmental monitoring. There is also potential for this technology in detection of mixtures of toxic chemicals that by themselves may not have severe effects, but in combination may have striking effects on human health. Molecular detectors would be highly valuable in these circumstances. The NIEHS is actively supporting research that will join the understanding of events that occur at the level of the living cell as a result of the action of environmental agents with the nanotechnology that you suggest.

Mr. Porter: Would it be part of NIEHS's mission to support the development and application of array sensors with molecular recognition capabilities of monitoring disease in human cells and tissues?

Dr. Olden: A major focus of the research mission of the NIEHS is to understand the effects of environmental agents at the molecular and cellular level. This understanding is fundamental to the prevention of human illnesses caused by exposure to environmental agents. Development of sensors that are so small and sensitive that they are capable of detecting chemicals at the cellular or tissue level is now on the scientific horizon. The Institute has an ongoing program on the development and validation of a variety of molecular biomarkers to monitor disease initiation, progression and promotion induced by environmental agents. The natural progression of this research is toward the microscopic level of sensors that will function at the cellular or tissue level.

LEAD AND HIGH BLOOD PRESSURE LINK

Mr. Stokes: Recently, the media has been reporting more and more on the link between high blood pressure, or hypertension, and high blood levels. Your Institute has a long history of involvement in research as it relates to the health effects of lead. What can you tell us about studies that are underway or planned to examine the link between hypertension and lead?

Dr. Olden: NIEHS supports considerable research relating to the health effects of lead both within our regular research portfolio as well as through research funded as a component of the Superfund Hazardous Substances Basic Research and Training Program. Interest in the topic of the interaction of lead and hypertension is shared between NIEHS and NHLBI.

We currently support a study using the participants in the 30-year longitudinal study of aging that is focused on the effects of lead, diet and blood pressure. The study assessed 590 subjects, all of whom had relatively low levels of blood lead. By careful statistical analysis of the data it was concluded that chronic lead accumulation, as measured by levels of lead in bone, may be a risk factor for developing hypertension in men in the general population.

Mr. Stokes: What are the implications of the studies' findings with regard to children suffering from lead poisoning and its impact on their long-term health?

Dr. Olden: It is well known that exposure to lead is deleterious to health at all ages. Clearly, these recent findings are provocative and provide additional evidence of the biological effects of this heavy metal. Lead is known to cause damage to the kidney and the resulting damage to the kidney stimulates elevation in blood pressure. Data from this study suggest that children with significant lead body burden show a substantial increase in the probability of developing irreversible hypertension as adults. This is an area of great public health concern. The NIEHS has had a long-term investment in basic research on the effects of lead. Fortunately, the Institute is now in a position to offer significant promise based on sound scientific principles for the remediation of lead in children and adults. We are now in the midst of a clinical trial of a lead chelating agent that has the potential of significantly reducing the body burden of lead. This clinical trial is focused on inner city children, the most likely group to suffer from exposure to lead.

COMMUNICATION "COMMUNITY GAP"

Mr. Stokes: Many communities that have borne the impact of environmental problems feel disenfranchised and ignored when these exposures are studied and assessed. Far too often, they are left ignorant of what findings and recommendations are made following exposure assessments. What is your Institute doing to correct this situation, to reach out, to inform and to involve, and empower local communities?

Dr. Olden: The NIEHS has initiated several approaches to better inform and empower local communities and to bring environmental health researchers and health care providers together with community outreach programs. The NIEHS promotes the involvement of our major programs, the Environmental Health Sciences Center program and the Superfund Hazardous Substances Basic Research and Training Program, with community groups in assisting and determining their future with respect to environmental public health by linking members of these communities with researchers. This consists, for example, of programs to increase public awareness, disease prevention programs, health professional training, primary, secondary and college general education, telephone inquiry and information programs, and community issue programs. In addition, NIEHS has established a program, "Environmental Justice: Partnerships for Communication," establishing links between members of a community with researchers and health care providers ensuring that the community has a role in identifying and defining problems and risks related to exposures. Further, NIEHS is establishing a program to develop community-based strategies aimed at prevention and intervention in economically disadvantaged and/or under served populations impacted by environmental contaminants. This program, "Community-Based Prevention/Intervention Research in Environmental Health Sciences," should enhance the knowledge and behavior of disadvantaged or under served community members, thereby reducing incidence and mortality rates of such diseases and conditions.

Our activities in minority/disadvantaged communities also include aspects of the Superfund Hazardous Waste Worker Training Program, especially the pilot study of Minority Worker Training. We believe that these programs are making an impact in affected communities, in terms of both awareness of problems and empowerment to address these problems as well as being trained for jobs in the environmental arena.

BREAST AND PROSTATE CANCER

Mr. Stokes: Breast cancer and prostate cancer are two of the major cancer killers in the nation. I understand that the Institute has made some significant discoveries regarding the genetic basis of these two diseases. Would you tell us about these discoveries and what they mean, and about the value of genetic findings to the activities which are under the purview of your Institute?

Dr. Olden: NIEHS researchers played a key role in the identification of the BRCA1 gene, which confers a profound predisposition to hereditary breast and ovarian cancer in women. This discovery makes possible the identification of high risk women by direct genetic screening. Initial studies indicate that women with identical genetic defects have highly variable disease outcomes. By comparing women with identical genetic risks, we are exploring gene-environment interactions in order to identify the elusive environmental factors in this critical women's health problem.

NIEHS scientists have also identified the KAI-1 gene, which appears to be a biomarker for the subset of prostate cancer that is life threatening. Expression of KAI-1 is decreased in men with metastatic prostate cancer, and reintroduction of this gene into rodent prostate cancer cells suppresses metastasis. Understanding alterations in KAI-1

expression associated with hazardous environmental exposures could eventually have important implications for disease prevention and, possibly, even for the development of novel therapeutic approaches.

CHEMICAL SIEGE

Mr. Stokes: I understand that there are thousands of chemicals in commercial use for which there is limited toxicologic information. Sometimes we appear to be under a chemical siege, with new chemicals being developed all the time, and seemingly with very little testing to assess their safety. What is the Institute doing to get a handle on this situation?

Dr. Olden: As you know, the NIEHS, through its National Toxicology Program (NTP) related activities, generates toxicological evaluations on chemicals of public health interest because of human exposure in the home, workplace and environment. It is estimated that there are 70,000 chemicals in commercial use today and adequate toxicological data is available on only 20% of them. Many of these chemicals were brought into commercial use prior to requirements, established by regulatory agencies, that the companies provide toxicological data necessary to make human safety assessments. The NIEHS systematically evaluates those chemicals in commercial use for which little or no toxicological data is available to determine which ones we should be studying in the NTP. Priority is given to those chemicals for which there is significant human exposure, and there is some indication such as reports in the literature, structure activity relationships, etc., that the chemical might be toxic to people. Chemicals selected for study are evaluated by a combination of approaches designed to gain information on carcinogenic activity as well as a number of non-cancer endpoints such as reproduction, birth defects, immune effects, neurotoxicology and hormonal actions.

Selection of chemicals is finalized after discussions with other Federal agencies such as EPA, FDA, OSHA, NIOSH, NCI, CPSC, ATSDR, and CDC to focus efforts on chemicals at greatest public health concern, to prevent duplication of effort, and to promote interagency efforts. The goal of these efforts is to provide regulatory agencies and the public scientific information necessary to make informed decisions regarding health hazards associated with chemical exposure.

Mr. Stokes: To what extent does the Institute have the opportunity to study the adverse health effects of these compounds.

Dr. Olden: The NTP rodent bioassay for chronic toxicity has been a major part of the NTP program since its inception. These tests are valuable but costly and time consuming, so we can only examine a limited number of chemicals each year with the resources available. To address this problem, we are making a significant commitment to the development and validation of new tests that are faster, cheaper, and more accurate. These tests include the use of transgenic animals and human cells, detection of chemical interactions with cellular molecules, computer evaluations of structure-activity relationships, and the use of non-mammalian species such as fish.

These new approaches, coupled with continued use of chronic rodent bioassays, will permit the NTP to generate toxicological evaluations on more chemicals than would be possible with chronic bioassay data alone. Furthermore, they will enhance our ability to more reliably estimate human risks from chemical exposures. Thus, a balanced program involving toxicology, human studies, basic research, biomathematics and communications with stakeholders will ultimately prove most useful in the protection of the public health.

INDUSTRY BENEFITS

Mr. Stokes: Doctor, as you know, many of the activities of federally supported research agencies benefit business and industry. I understand that some of the Institutes have partnerships and agreements with business and industry. Can you tell us if your Institute has such agreements or if you have considered the benefits of public-private partnerships in the development and support of research projects.

Dr. Olden: The National Toxicology Program is an important component of a coordinated government/academic and private industry effort in chemical toxicity evaluations. Although co-funding studies by combining monies has not been common, cost sharing has occurred through other means and informal partnerships have been a normal course of business.

Recently, the NTP has initiated efforts to establish more formal partnerships. We are focusing on three projects which are being developed cooperatively with interested industry, academic and other groups. One involves the worldwide coordination of the evaluation of several different transgenic mouse models for carcinogen identification; a second involves the creation of an entity which would carry out an unbiased scientific review of agents or substances thought to pose a threat to human reproduction and development, and the third promotes the development and regulatory agency acceptance of toxicology test methods that reduce the numbers of animals required, and provide approaches for generating more accurate, faster and less expensive toxicological evaluations. All three efforts will, if successful, benefit the toxicology and regulatory community as well as affected industries.

HEALTH STATUS AND ENVIRONMENTAL INEQUITY

Mr. Stokes: I am concerned that the health status of socioeconomically disadvantaged populations is not nearly as good as that of the rest of the nation. Though access to health care is probably a component to this problem, environmental and occupational exposures also appear to play a role in the health status equation. Could you tell this committee how your Institute is addressing this problem?

Dr. Olden: Socioeconomically disadvantaged populations are more likely to be occupationally exposed to hazardous chemicals, to live near hazardous waste sites, and to be in environments with polluted air and water. For these reasons, NIEHS has a clear interest in providing research that can improve the health of these populations. The NIEHS conducts research on lead poisoning and treatment in disadvantaged populations through several mechanisms. The Developmental Center grants program and the Institute of Medicine Study has attracted outstanding scientists to use their talents and cutting edge technologies to address the likely causal association between the disproportionate exposure to environmental agents and excess morbidity and mortality among socioeconomically disadvantaged populations. Moreover, the NIEHS provides environmental justice grants to fund health research projects that support minority and low-income communities.

Mr. Stokes: A far higher percentage of African-Americans and Hispanics live in areas that exceed national air quality standards for major pollutants such as carbon monoxide, ozone and lead. What is the NIEHS doing to remedy this environmental inequity?

Dr. Olden: Particulate air pollutants are of great public health importance particularly in urban environments. These come mainly from industrial sources and automotive air pollution. Although it is not within the purview of the NIEHS to deal with the social and economic issues of housing and occupational locations of minority populations, we are engaged in research to address health implications of the issue. First, the NIEHS supports a broad portfolio of basic and applied research directed towards the identification and prevention of adverse health effects from air pollution. One such study is underway to evaluate the risks among inner-city minority children for increased exposure to air pollutants and increased sensitivity compared to white suburban children. It is referred to as the 5-Cities Study. Specifically, the study is designed to assess (1) the chronic effects of air pollution on respiratory health of children, (2) acute effects of summer air pollution episodes on respiratory health of children, (3) relationships of air pollution episodes with increased emergency department visits for respiratory complaints, and (4) the associations of daily air pollution exposures and daily mortality.

Recently, the NIEHS joined with the NIAID in sponsoring an RFA in support of the National Cooperative Inner-City Asthma Study. The goal of this study is to design and evaluate asthma intervention strategies in under served inner-city children and adolescents from 4 - 12 years of age. The NIEHS is focusing its efforts in this study on the environmental components of the intervention plan. Applications in response to this RFA have been received and reviewed. Awards are scheduled to be made before the end of this fiscal year.

The second part of this effort is the NIEHS program on Environmental Justice-Partnerships for Communication. As I indicated earlier, this program has as its central theme involvement of local communities and community groups in research focused on health problems endemic to those population groups.

GENE REPOSITORY

Mr. Stokes: What is the association between genetic predisposition and the research under the purview of your Institute?

Dr. Olden: The impact of all or almost all environmental agents is determined by the combination of the exposure and of individual susceptibilities. Susceptibility in turn is determined by a mixture of age and gender, previous history of exposure to many environmental agents, and genetic predisposition. An understanding of genetic predisposition is important in virtually all NIEHS research.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are underway at your Institute? Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Olden: NIEHS is currently conducting only one clinical trial, the Treatment of Lead-exposed Children Trial. It is designed to determine whether an oral drug that lowers blood lead levels will prevent the delays in cognitive development, slowed growth, and behavior disorders caused by lead poisoning in young children. The budgets for this trial in FYs 94-97 are \$6.4, 6.4, 5.2, and 5.7 million, with about half of the funding coming to us from the Office of Research on Minority Health. The budget also includes funding of \$250 thousand each year in FY 1996 and FY 1997 for a pilot study on the primary prevention of asthma in children.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: What progress do you have to report this year with respect to activities underway at your Institute that are designed to address the gap in minority health? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Olden: The NIEHS strongly supports research aimed at achieving environmental equity for all populations. Assays of the health effects of environmental pollution, as well as regulations based on such assays, are often performed with little or no input from the affected community. The NIEHS is able to bridge this crucial communication gap through its *Environmental Justice: Partnerships for Communication* grant program. The main objective of this program is to establish a new research paradigm linking members of the community, who are directly affected by adverse environmental conditions, with researchers and health care providers. Seven awards span a spectrum of affected populations including Asian/Pacific Islander, African-American, Hispanic, and Native American communities. This effort has successfully heightened the awareness of the role of biomedical research and defined a new standard for outreach to minority communities by environmental health science centers and researchers.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African-American and other minority research investigators involved in research under the purview of your Institute?

Dr. Olden: The NIEHS is committed to aggressively recruiting African-American and other minorities into research careers. The Institute has intramural and extramural programs that focus on these populations at all points in their educational experience. In the intramural programs we have been very active in recruiting summer students into our laboratories and have reached out to numerous predominantly minority institutions in and around the Research Triangle Park. The Institute has also made great progress in our permanent staff. When I came to NIEHS in 1991 there was a total of six doctoral level scientists who were African-American, Hispanic or Native American and only one of them was tenured. We now have fifteen of these minority scientists and six are tenured so I think we are doing well. We have also increased the number of women in our upper ranks and have recently appointed one female branch chief and are in the process of appointing another. In the extramural arena, we support active programs that reach beyond the bounds of the Institute and offer opportunities for minority students and scientists throughout the country.

One recent activity is reflective of substantial success that aggressive efforts in this area have achieved. The NIEHS sponsored a workshop for minorities who are currently supported by NIEHS projects and are at the postdoctoral level. The goal of this workshop was to provide them with information on career opportunities as well as to work with them on the development of a research grant application. I am pleased to report that even in this short time two have achieved success, one has already been awarded a First Independent Research Support and Transition Award and another applicant has done exceptionally well and is likely to be awarded before the end of this fiscal year.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Olden: The Institute's significant outreach and public education programs include the K-12 Science Education, Centers, Environmental Justice and Community Based Prevention Intervention Research Programs, the Summers of Discovery Program and a variety of programs conducted by the office of the Director that include symposia, scientists-in-the classroom activities, student and adult group visits and tours to the NIEHS, a variety of internships at different educational levels, technical assistance to local groups and the NIEHS ENVIROHEALTH/EMF Hotline. The NIEHS has

spent \$1.4 million and \$1.6 million respectively on these activities in FY 1994 and FY 1995. In FY 1996, approximately \$2.1 million will be provided and a similar amount is planned for FY 1997. Additional funds have been provided each year by the Office of Research on Minority Health (ORMH), NIH.

Mr. Stokes: In most of the Institutes, these programs are funded in research management and support accounts, is this the case in your Institute? If so, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are you hurting the most?

Dr. Olden: At NIEHS, outreach is an integral part of almost all of our activities; public information, Intramural research where our scientists speak to students and civic groups and have adopted a local school; grants where our centers have an outreach component directed to their local area; environmental justice projects funded primarily from the Office of the Director, and others. Those pieces that are funded from Research Management and Support have taken their share of the reduction and this has required a cutback in support for conferences and workshops, travel to meet with community groups, and limited distribution of public information.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between your Institute and the office of research on minority health? Are there specific projects in your Institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of these projects, include their period of performance, and the percentage and the amount of funding provided for each.

Dr. Olden: There are a number of activities on which we collaborate with the ORMH where the funding comes totally from ORMH. These are generally those where the project starts with a health problem that seems to affect minorities exclusively or predominantly and attempts to determine what role environmental factors play. Of course, this is not always a clear line and in all cases the Institute provides the people who direct and administer the projects so we always provide some of the resources. Those projects that receive all of their funding from ORMH include:

NIEHS/ORMH
Collaborative Projects

Research Categories and Project Titles	Period of Performance	ORMH Contribution
Environmental Justice		
Environmental Justice: Partnerships for Communication (R25)	94-96	\$1,704,466
Institutional Capacity Building		
Developmental Grant: Environmental Health Science Centers	94-96	\$1,650,001
Training & Education Workshops		
Minority Faculty Developmental Award (K14)	94-96	\$576,673
Short Term Research Training for Minority Students (T35)	94-96	\$230,619
Additional Smaller Activities	95-97	\$213,000

Mr. Stokes: Are there specific projects that are co-funded by the Institute; and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Olden: Yes, there are some projects where we employ co-funding. Normally these are projects where the primary focus is on understanding environmental causes of disease that impact everyone, but which may have a specific element unique to minorities. In these cases, NIEHS would fund the basic project and ORMH would fund those parts that relate primarily to minorities.

NIEHS/ORMH
Co-Funded Projects

Research Categories and Project Titles	Period of Performance	NIEHS Contribution	ORMH Contribution
Lead Poisoning and Treatment			
Lead Clinical Trial	93-99	\$13,966,632 46%	\$16,360,644 54%
Biokinetics of Lead in Human Pregnancy	90-97	\$1,404,258 44%	\$1,823,898 56%
Biokinetics of Lead in Non-Human Primate Pregnancy	90-95	\$1,293,836 55%	\$1,041,340 45%
Training & Education Workshops			
Supp. Funding Alliance for Minority Participation Grant: UMBC (Meyerhoff Program)	95-99	\$600,000 24%	\$1,900,000 76%
Environmental Science and Management Fellows-IAG, Tufts University	93-95	Provided 1 yr. Internships @ NIEHS facility	\$224,520
IOM Study on Environmental Justice: Research, Education, and Health Policy Needs	95-97	\$136,000 73%	\$50,000 27%

GENE THERAPY

Mr. Stokes: How critical is gene therapy research to furthering advances in areas of research which are under the purview of your Institute? What diseases and disorders would benefit from enhanced research in this area?

Dr. Olden: Gene therapy results with some specific forms of genetic diseases including cancer are very encouraging. For example, breast and ovarian cancer patients may well eventually benefit from gene therapy with the BRCA1 protein. Holt et al. (*Nature Genetics* 12: 298-302, 1996) have recently shown that a retrovirus vector encoding the normal BRCA1 gene product can suppress the growth of several breast and ovarian cancer

cell lines in vitro. These observations were extended to demonstrate that the normal BRCA1 virus could also suppress tumor formation of a specific breast cancer cell line in nude mice. Based on these preliminary studies, a Phase I clinical trial has just been initiated by the Vanderbilt scientists to see if the BRCA1 vector can benefit ovarian cancer patients with advanced stage disease. While these preliminary results are exciting, they will require further studies and confirmation by independent scientists before they can be accepted as general cancer therapy.

Here at the NIEHS we are planning, for example, to pursue the development of gene therapy based on the KAI-1 prostate cancer metastasis suppressor gene. Other areas of potentially fruitful gene therapy research, which will also be important from an environmental perspective, will certainly emerge as additional genetic susceptibilities are identified by Institute scientists and other researchers in the field. One category of susceptibility genes that clearly holds great promise for such research involves those genes that regulate metabolism. For example, the superoxide dismutase family has been implicated in a number of diseases, and there are genetic predispositions that show deficiencies in these proteins that might well be rectified by gene therapy.

ASTHMA

Mr. Hoyer: Asthma is one of the most prevalent chronic childhood diseases. Despite the best efforts of talented scientists and researchers, we still seem to be very far from discovering a cause of a cure for this condition. Is asthma research a priority for the NIEHS? What are you doing to determine the environmental components of this disease? How are you collaborating with other NIH Institutes to address this problem?

Dr. Olden: The NIEHS has a strong interest and a historical commitment to studying the basic scientific relationship between air pollutants and asthma. We are particularly interested in mechanistic studies, utilizing animal models, cultured human cell models and human patients to understand the environmental components of asthma.

Two other Institutes of the NIH have substantial portfolios of research in this important area. They are the National Heart, Lung, and Blood Institute and the National Institute of Allergy and Infectious Diseases. Because this is an area in which there is overlapping scientific interest and support, the NIEHS has been cooperating with both Institutes in joint research announcements and continues to share scientific information.

Mr. Hoyer: I understand from news reports that increasingly, adults are developing asthma, allergies, and other health conditions that did not affect them earlier in life. Many suspect that environmental factors may play an important role in this. Can you comment on this trend and the research your Institute is conducting in this regard?

Dr. Olden: Many of the illnesses that seem to have been caused or exacerbated by exposure to environmental agents and manifest themselves in adulthood have roots in the early years of life. One major focus on asthma within the NIEHS is in connection with the National Cooperative Inner-City Asthma Study, in cooperation with the NIAID. The objective of this cooperative study is to develop, implement and evaluate a culturally-appropriate, comprehensive and cost-effective intervention program aimed at reducing asthma morbidity by modifying those potentially reversible factors shown to contribute to asthma morbidity, such as lack of access to medical care, poor self-management skills and environmental exposures. This study focuses on under-served children and adolescents. We know that once sensitized, the asthmatic condition persists into adulthood and beyond.

COORDINATION OF ENVIRONMENTAL POLICY

Mr. Hoyer: How does your Institute work with EPA, NSF, and other governmental and non-governmental agencies to coordinate your research and inform public debate over environmental policy?

Dr. Olden: Coordination is clearly important and, as your question implies, involves both governmental and nongovernmental entities. The NIEHS participates in many activities that ensure coordination in research efforts and serve to inform the public. Formal mechanisms include participation in the Committee on Environmental and National Resources (CENR), under the purview of the cabinet-level National Science and Technology Council (NSTC). NIEHS is an active participant in the CENR subcommittees created to address particular issues, including the most recent one on Endocrine Disruptors. Participants in CENR are drawn from across government and include EPA, Commerce (NOAA), and NSF. Within HHS, the Environmental Health Policy Committee (EHPC), of which NIEHS is a key member, provides a significant forum for research and policy coordination and includes as liaison members the USDA, EPA, DOE, DOT, and DOD. The NIEHS also recognizes the need to include not only our sister federal institutions with an environmental research agenda, but also the many stakeholders outside of government, including industry, labor unions, environmental advocates, and community organizations. Members of these groups are routinely invited to serve on our Advisory Councils and Boards. The information exchanges fostered by these formal meetings provide a useful link to these nongovernmental groups; not only does the NIEHS receive the benefit of a nongovernmental point of view in its deliberations on mission and research direction, but the representative is in a good position to take information about NIEHS research activities back to his/her organization. In addition to these formal committee structures, the NIEHS convenes and participates in ad hoc scientific workshops and conferences focusing on specific research areas, especially in fast-evolving fields. These meetings provide a forum for scientists to interact, exchange information, and form collaborations that move research ahead more fully and productively. Those attending include scientists from NIEHS, other NIH institutes, other Public Health Services agencies such as CDC and ATSDR, other Federal agencies, and academic centers, universities, and research institutes. Some of these, such as the environmental justice symposium co-sponsored by NIEHS, bring together not only scientists, but also lay public and policy makers. In this way the NIEHS serves to foster a more informed public debate on environmental policy issues and research needs.

JUSTIFICATION OF THE BUDGET ESTIMATES

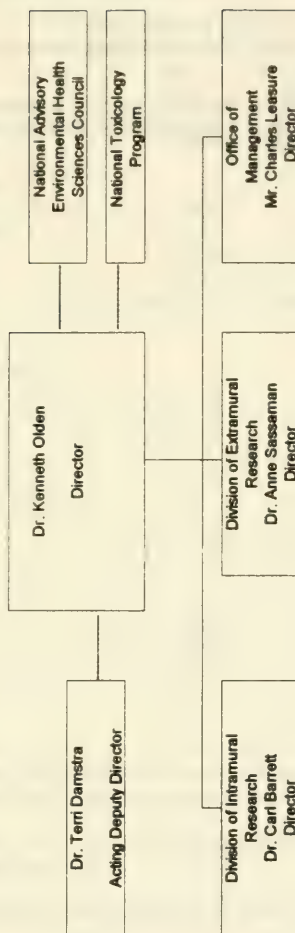
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

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NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

For carrying out section 301 and 311 and title IV of the Public Health Service Act with respect to environmental health sciences, \$289,114,000.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$267,566,000	\$288,898,000	\$289,114,000
Reduction in accordance With P.L. 103-333.....	-578,000		
Rescission in accordance With P.L. 104-19.....	-422,000		
Subtotal, Adjusted Appropriation.....	266,566,000	\$288,898,000	\$289,114,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-229,000		
Comparative transfer to Office of AIDS Research, NIH for HIV activities.....		-6,051,000	
Subtotal, adjusted Budget authority.....	266,337,000	282,847,000	289,114,000
Unobligated balance, lapsing.....	-70,000		
Total obligations.....	266,267,000	282,847,000	289,114,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1995—\$90,857,000; FY 1996—\$81,263,000; FY 1997—\$81,263,000.

Also excludes funding for HIV activities: FY 1995—\$5,745,000; FY 1997—\$6,028,000, included in the Office of AIDS Research, NIH.

Note: Excludes \$54,000 in FY 1995 and \$153,000 in FY 1996 for royalties.

Justification

National Institute of Environmental Health Sciences

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
654	\$266,337,000	671	\$282,847,000	671	\$289,114,000	--	+6,267,000

Introduction

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute of Environmental Health Sciences (NIEHS). Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The mission of the NIEHS is to reduce the burden of environmentally associated diseases and dysfunctions by understanding (1) how environmental exposures affect our health, (2) how individuals differ in their susceptibility to these exposures, and (3) how these susceptibilities change as a function of time and age. To fulfill this mission, the Institute provides the science that is necessary to understand the impact of the environment on human health, translates this information into prevention and intervention strategies, and communicates this information to the American public.

The mission of the NIEHS, though formidable, is extremely important. Diseases and dysfunctions with an environmental component include cancer, birth defects, infertility, neurological impairments, immune disorders, and lung dysfunctions. Because environmental exposures can be controlled or avoided, they represent one of the most promising means of improving our Nation's health. The NIEHS will have an increasingly important role as public policy makers struggle to balance human health needs with the economic benefits of commercial processes that might endanger that health. Their decisions will only be as good as the scientific foundation upon which it rests.

Stories of Discovery

Environmental health research is at a critical and exciting juncture. New refinements in molecular biology techniques provide unprecedented opportunities for understanding the molecular and cellular basis of environmentally associated diseases. These opportunities build upon the foundation of almost thirty years of research supported or conducted by the NIEHS. Three recent discoveries - identification of a prostate cancer metastasis gene, the behavioral effects of environmental lead, and promising molecular interventions for environmentally caused cancers - are highlighted below.

Prostate Cancer Metastasis Gene: For men, prostate cancer is arguably their greatest cancer fear. Not only does it account for one in every four cancers diagnosed in American men, but it can spread (metastasize) beyond the prostate, killing 40,000 men annually. Although only 25% of these cancers are the lethal variety, physicians have no way of determining which prostate cancers can be ignored and which must be surgically removed. This dilemma is further complicated by the fact that prostate cancer surgery is a difficult surgery, requiring a lengthy recovery time and frequently rendering a man incontinent or impotent. A biological marker that identifies which patients are truly at risk of the cancer spreading beyond the prostate, and thus meriting surgery, would prevent unnecessary surgeries among men with non-metastatic prostate cancers. NIEHS intramural researchers, working with colleagues at John Hopkins University, have isolated the first such marker. This gene, KAI1, was shown to suppress the spread of prostate cancers in experimental animals and it appears to be lost in metastatic human prostate cancers. Its discovery will initially lead to better identification of patients requiring prostate cancer surgery. Its identification also enhances our ability to develop therapeutic strategies to more effectively treat this devastating disease. Ultimately, studies on this gene will help us identify the environmental components leading to prostate cancer development, thus enabling us to help completely prevent its development in the first place.

Lead Exposure, Its Link to Criminal Behavior, and Its Treatment: Adult criminality, alcoholism, and domestic abuse are on the rise. Our Nation's citizens are concerned for their safety and demanding these problems be remedied. Interestingly NIEHS' long history of research is revealing an unanticipated environmental component to these social problems - lead. NIEHS-supported researchers have shown that the developing fetus and young child are particularly susceptible to lead and that their brain is the most vulnerable target. Further research, published in 1990, revealed that even at exposures previously thought to be safe, young children suffer from measurable decreases in IQ scores and exhibit anti-social and delinquent behavior. A new study on a cohort of young boys in Pittsburgh's inner city confirms that above-normal lead levels are associated with more aggressive and delinquent behavior, such as bullying, vandalism, theft, fighting, and setting fires. These behaviors foreshadow the development of more serious problems as these boys become adults, including adult criminality, alcoholism, and domestic abuse. It is notable that inner city environments, which are known to have high crime rates, also suffer from high levels of environmental lead. These studies suggest a need for enhanced lead prevention programs as part of a strategy to improve public safety.

Other important research explores ways to prevent lead being absorbed and to intervene or reverse neurobehavioral consequences once this exposure has occurred. One study supported by the NIEHS and the NIH Office of Research on Minority Health is examining the ability of a chelating drug, succimer, to prevent or reverse the neurobehavioral effects of low blood lead levels in young children. Other researchers are determining how much of a child's lead burden is determined by its most important environment - its mother. Lead stored in a woman's bones can be mobilized during pregnancy and lactation, then transferred to the fetus or suckling child. This early lead exposure might be one of the most significant lead sources for children, suggesting that early testing and treatment of pregnant women is an important component of reducing lead exposure in children. Results from these ongoing studies will provide vital information in

constructing a prevention program to protect our children from the consequences of lead exposures.

Molecular Prevention/Intervention of Environmentally Induced Cancers: DNA repair proteins are one of the body's most important defenses against environmental cancer-causing agents (carcinogens). NIEHS extramural and intramural scientists have been actively engaged in studying this vital protective mechanism. This research has tremendous potential in being used to develop molecular intervention techniques, as was recently demonstrated by NIEHS extramural researchers. These scientists developed a transgenic mouse that can be made to overexpress a specific human DNA repair gene, *O*⁶-alkyl guanine-DNA alkyl transferase. Using this transgenic model, investigators can study the ability of a human DNA repair protein to help resist tumor induction by common environmental carcinogens. In one set of experiments, mice overexpressing this human gene in the thymus had a dramatically reduced incidence of lymphoma/leukemia following exposure to methylnitrosourea. When the DNA repair gene was introduced into the colon, treated mice had a reduced incidence of induced precancerous foci in the colon. When this gene was overexpressed in the lung, the mice were protected from the lung tumor-induction properties of a tobacco smoke carcinogen. Mice which over-expressed this gene in the liver were protected from development of liver tumors following exposure to dimethylnitrosamine, a common environmental and industrial pollutant. In each instance, overexpression of the gene in the corresponding tissue provided tissue specific protection from the methylating carcinogen. This work has important implications not only for developing therapeutics that protect against environmentally caused cancers, but also as a technique that could protect the body against some of the biological damage inflicted by chemotherapy during cancer treatments.

Annual Scientific Advances

This past year has shown the fruition of many year's of NIEHS-supported research in some of the most promising areas of environmental health. Highlights of these discoveries follow.

"Knock-out" Mice Provide Insight into Causes and Treatments for Colon Cancer, Arthritis, and Inflammatory Diseases: Aspirin, one of the oldest manufactured drugs, has been hailed as a "wonder drug" in the treatment of arthritis, colon cancer, and inflammation. The usefulness of aspirin and related drugs are limited, however, by such side effects as ulcers and kidney damage. It is known that these drugs act by blocking two enzymes, COX-1 and COX-2. NIEHS researchers and scientists at the University of North Carolina at Chapel Hill have succeeded in developing two strains of transgenic mice, each lacking the gene for one of these enzymes. These enzymes are believed to play a role in the development of colon cancer and arthritis. Studies with these mice will lead to a better understanding of inflammatory diseases, arthritis and colon cancer as well as better drugs to treat them.

Breast Cancer Susceptibility Gene - In the fall of 1994, the long-sought human breast cancer susceptibility gene, BRCA1, was identified by a team of researchers at NIEHS, the University of Utah, and a private company, Myriad Genetics. Scientists are using this information to develop assays that will detect BRCA1 mutations and enable physicians to counsel women about their individual risk of breast cancer. Although BRCA1 was originally

thought to account for 5% of breast cancer cases, researchers are now finding that altered BRCA1 expression may account for many more breast cancer cases.

This year intramural scientists at NIEHS characterized the mouse BRCA1 gene. This work will enable us to develop a mouse model, providing researchers with an important tool for studying this critical gene, identifying potential breast carcinogens, and developing therapies for this devastating disease.

Cancer-Causing Potential of Common Laxatives - We all buy products over-the-counter which we assume to be safe. Some of the ingredients, however, were developed prior to current regulatory testing requirements. The NIEHS, under the auspices of the National Toxicology Program (NTP) conducts long-term tests in rodents on some of these common, but untested, compounds. Phenolphthalein, the active ingredient in many nonprescription laxatives, was tested and found to be carcinogenic in both rats and mice. This finding is particularly disturbing because laxatives are often abused and many people use them for long periods of time, even though the manufacturers advise against this practice. The public health impact of this discovery is obvious. Based on these findings, manufacturers are now replacing phenolphthalein with other, more benign, laxative agents.

DES Sons' Fertility - Diethylstilbestrol (DES) is a synthetic estrogen once used to prevent miscarriages. Its use has been banned since the 1970s when it was shown to increase the risk of vaginal cancers in daughters who were exposed during their mother's pregnancy. One unanswered question has been "What were the health consequences to the sons who were exposed during their mother's pregnancy?" Many exhibited genital defects at birth, but no one knew if these defects would translate into infertility problems later. A recent epidemiologic study conducted by NIEHS intramural scientists should allay these fears. Although DES sons had three times the number of genital malformations as did the unexposed control group, there was no evidence that DES impaired their ability to father a child.

Improved Risk Assessment - Traditional risk assessments are based on results of two-year rodent assays. The time and expense of these assays restricts our ability to screen large numbers of chemicals. This fact is significant because there are currently 70,000 chemicals in commerce with little or no toxicologic data. It is also important to pharmaceutical and chemical companies because it adds to the time and cost of development for new products. Reducing the time required for a cancer bioassay from two years to six months means that new treatments for patients will be available sooner. The reduced development costs and the extra eighteen months of revenues and profits while a drug is under patent, would improve financial incentives for more private research and development in this area.

The NIEHS, under the auspices of the National Toxicology Program (NTP), is on the threshold of developing and validating new animal models and test systems that reduce the current dependency on two-year rodent assays. Preliminary results on two commercially available transgenic mice indicate that reliable data can be generated more rapidly and at less cost using these mice. Such test systems will allow for screening of dozens of chemicals annually and the results will be more relevant for the assessment of risk to human health.

Pursuing this avenue is irrelevant, however, if the regulatory structure can not be modified to accept alternative test models. For this reason, NIEHS has taken the leadership role in building consensus among all relevant stakeholders for this new concept. These stakeholders include industry, regulators, unions, environmental advocacy groups, and toxicologists. The recent workshop "Validation and Regulatory Acceptance of Alternative Toxicological Test Methods" was productive and the NIEHS is now developing partnerships with industry to help defray the costs of validating some of these novel test systems.

Benefits and Impact of Research

Understanding the environmental components and basic biology of disorders can lead to prevention and intervention strategies that circumvent many adverse health effects. Traditionally these strategies have focused on eliminating or reducing environmental exposures. These approaches will continue to be important parts of the Nation's environmental health programs. NIEHS is working to improve risk assessment methodology so that regulation is not needlessly restrictive, but rather protects both public health and economic vitality.

As we understand the molecular and cellular basis of environmentally associated diseases, prevention and intervention techniques could be developed to treat people following an adverse environmental exposure. These molecular intervention techniques would rely on manipulations of the biological mechanisms underlying environmentally induced diseases, such as activating and inactivating enzymes, receptors, and other molecular components. They would be particularly useful in dealing with environmental exposures that are ubiquitous or difficult to eliminate. Further, they would have important implications in the pharmaceutical and pesticide industries, which could in the future develop products with maximal effectiveness and minimal side effects.

Budget Policy

The FY 1997 budget request for NIEHS is \$289,114,000, an increase of \$6,267,000 over the FY 1996 estimate. Seventy-one percent of the budget request would support research grants, training, and contract activities, and 29 percent of the request would support intramural research and research management activities.

In the FY 1997 President's Budget Request, NIEHS support for research project grants (RPGs) would increase by 5.3 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 157 competing RPGs, an increase of 20 competing RPGs over FY 1996, and 495 total RPGs, an increase of 36 total RPGs over FY 1996.

Seventeen environmental health sciences centers and five marine and freshwater biomedical sciences centers would receive \$22,290,000 in support from this request, an increase of \$568,000

over FY 1996. Other research grants would receive \$5,497,000, an increase of \$200,000 over FY 1996.

The FY 1997 request would support 482 research trainees at an estimated cost of \$11,205,000, an increase of \$241,000 over FY 1996.

Contracts to support research and development in toxicity testing and test development, in risk estimation methods, and for other scientific problems in environmental health are projected at \$60,218,000. Approximately 108 contracts would be supported, a decrease of \$750,000 from FY 1996.

The budget request for intramural research is \$74,210,000 and 568 FTEs, an increase of \$650,000 over FY 1996. The request for research management and support is \$9,037,000 and 103 FTEs, the same as FY 1996.

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Research Projects:						
Noncompeting	300	\$70,818,000	301	\$68,654,000	313	\$68,530,000
Administrative supplementals	(9)	520,000	(10)	538,000	(10)	538,000
Competing:						
Renewal	40	10,283,000	42	10,131,000	57	12,586,000
New	53	8,780,000	94	18,990,000	99	21,397,000
Supplementals	1	67,000	1	17,000	1	22,000
Subtotal, competing	94	19,130,000	137	29,138,000	157	33,985,000
Subtotal	394	90,468,000	438	98,330,000	470	103,053,000
SBIR/STTR	15	2,571,000	21	2,969,000	25	3,604,000
Subtotal, RPG	409	93,039,000	459	101,299,000	495	106,657,000
Research Centers	22	21,072,000	22	21,722,000	22	22,290,000
Other Research:						
Research career programs	23	2,728,000	23	2,839,000	23	2,839,000
Minority biomed res. support	--	463,000	--	462,000	--	462,000
Other research related	12	1,585,000	15	1,996,000	15	2,196,000
Subtotal, other research	35	4,776,000	38	5,297,000	38	5,497,000
Total, Research Grants	466	118,867,000	519	128,318,000	555	134,444,000

Training						
Individual awards:						
Noncompeting.....	22	570,000	23	714,000	23	728,000
Competing:						
New.....	21	562,000	23	447,000	23	456,000
Subtotal, individ.....	43	1,132,000	46	1,161,000	46	1,184,000
Institutional awards:						
Noncompeting.....	332	7,356,000	420	9,543,000	330	7,078,000
Competing:						
Renewal.....	80	2,280,000	9	165,000	92	2,844,000
New.....	19	96,000	7	95,000	14	99,000
Subtotal, inst.....	431	9,732,000	436	9,803,000	436	10,021,000
Total, training.....	474	10,864,000	482	10,964,000	482	11,205,000
Research & Development						
Contracts (SBIR/STTR).....	104 (7)	56,692,000 (1,240,000)	108 (7)	60,968,000 (1,240,000)	108 (9)	60,218,000 (1,575,000)
Intramural Research.....						
	FTEs		FTEs		FTEs	
	552	70,124,000	568	73,560,000	568	74,210,000
Research Management and Support						
	102	9,770,000	103	9,037,000	103	9,037,000
Total, NIEHS.....						
	654	266,337,000	671	282,847,000	671	289,114,000
Clinical Trials.....						
		(3,127,000)		(3,087,000)		(2,868,000)

Note. Includes 10 FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Activity
(Dollars in thousands)

	1993 FTEs Amount	1994 Actual FTEs Amount	1995 Actual FTEs Amount	1996 Estimate FTEs Amount	1997 Estimate FTEs Amount	Change FTEs Amount
Extramural Research:						
Biological response to environ agents.....	\$75,154	\$82,336	\$82,130	\$88,977	\$93,317	+\$4,340
Applied toxicologi- cal res. and testing.....	53,336	54,861	62,235	68,526	68,585	+59
Biometry and risk estimation.....	8,943	10,527	10,142	10,061	10,470	+409
Resource and man- power development.....	27,986	30,847	31,936	32,686	33,495	+809
Subtotal.....	165,419	178,571	186,443	200,250	205,867	+5,617
Intramural research.....	653	72,226	599	70,299	568	73,560
Research management and support.....	97	9,138	103	9,639	103	9,037
Total obligations.....	750	246,783	702	258,509	671	282,847
Unobligated balance lapsing.....	--	132	--	132	--	--
Total Budget Authority.....	750	246,915	702	258,641	671	282,847
			654	266,337	671	289,114
						+6,267

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Summary of Changes

1996 Estimated budget authority.....	\$282,847,000
1997 Estimated budget authority.....	289,114,000
Net change.....	+6,267,000

	1996 Current	Change from Base
	Estimate Base Budget (FTEs) Authority	Budget (FTEs) Authority
Changes		
A. Built-in		
1. Intramural research:		
a. Within grade increases.....	\$37,024,000	+\$593,000
b. Annualization of January 1996 pay increases.....	37,024,000	+235,000
c. January 1997 pay increases	37,024,000	+833,000
d. Increase in unemployment compensation.....	225,000	+9,000
e. Decreased cost of centrally furnished services.....	2,168,000	-149,000
f. Increased cost of Service and Supply Fund.....	1,691,000	+37,000
g. Increased cost of laboratory supplies, materials, and other expenses	32,452,000	+719,000
Total.....		+2,277,000
2. Research management and support:		
a. Within grade increases.....	5,532,000	+98,000
b. Annualization of January 1996 pay raise.....	5,532,000	+35,000
c. January 1997 pay raise	5,532,000	+124,000
d. Increased cost of centrally furnished services.....	1,127,000	+39,000
e. Increased cost of Service and Supply Fund.....	93,000	+2,000
f. Increased cost of laboratory supplies, materials, and other expenses...	2,285,000	+50,000
Total.....		+348,000
Subtotal.....		+2,625,000

Summary of Changes—continued

	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting.....	301	69,192,000	+12	-124,000
b. Competing	137	29,138,000	+20	+4,847,000
c. SBIR/STTR.....	21	2,969,000	+4	+635,000
Total.....	459	101,299,000	+36	+5,358,000
2. Centers.....	22	21,722,000	+22	+568,000
3. Other research.....	38	5,297,000	--	+200,000
4. Research training.....	482	10,964,000	--	+241,000
5. Research and development contracts.....	108	60,968,000	--	-750,000
Subtotal, extramural.....				+5,617,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic decreases.....				-2,277,000
b. Special emphasis areas.....				+650,000
Total.....	568	73,560,000	--	-1,627,000
7. Research management and support.....	103	9,037,000	--	-348,000
Subtotal, program.....				+3,642,000
Total changes.....				+6,267,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs included in the Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment.....	671	671	--
Full-time equivalent of overtime and holiday hours	4	4	--
Average ES salary.....	\$115,714	\$119,185	+\$3,471
Average GM/GS grade.....	10.69	10.69	--
Average GM/GS salary	49,823	52,812	+2,989
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).....	73,857	76,073	+2,216
Average salary of ungraded positions.....	42,476	43,750	+1,274
Personnel compensation:			
Full-time permanent	\$26,642,000	\$27,292,000	+\$650,000
Other than full-time permanent.....	5,245,000	5,326,000	+81,000
Other personnel compensation.....	621,000	640,000	+19,000
Special personnel service payments.....	3,561,000	3,613,000	+52,000
Total personnel compensation.....	36,069,000	36,871,000	+802,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Personnel benefits.....	6,462,000	6,582,000	+120,000
Benefits for former personnel.....	25,000	25,000	--
Travel and transportation of persons.....	1,269,000	1,284,000	+15,000
Transportation of things.....	185,000	160,000	-25,000
Rental payments to GSA.....	540,000	540,000	--
Rental payments to Others.....	610,000	610,000	--
Communications, Utilities, and Miscellaneous Charges.....	4,842,000	5,542,000	+700,000
Printing and reproduction.....	821,000	775,000	-46,000
Other services			
Consulting services.....	151,000	153,000	+2,000
Other.....	13,591,000	13,298,000	-293,000
Purchases from Govt. Accts.....	6,061,000	5,950,000	-111,000
R&D contracts.....	60,968,000	60,218,000	-750,000
Supplies and materials.....	7,816,000	7,358,000	-458,000
Equipment.....	4,150,000	4,094,000	-56,000
Grants, subsidies & contributions.....	139,282,000	145,649,000	+6,367,000
Interest and dividends.....	5,000	5,000	--
Total budget authority by object.....	282,847,000	289,114,000	+6,267,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Administrative Costs

	1996 Estimate	1997 Estimate	Increase or Decrease
Personnel compensation:			
Full-time Permanent (11.1).....	\$26,642,000	\$27,292,000	+\$650,000
Other than Full-time Permanent (11.3).....	5,245,000	5,326,000	+81,000
Other Personnel Compensation (11.5).....	621,000	640,000	+19,000
Special Personnel Compensation (11.8).....	<u>3,561,000</u>	<u>3,613,000</u>	<u>+52,000</u>
Total Personnel Compensation.....	36,069,000	36,871,000	+802,000
Personnel benefits (12.1).....	6,462,000	6,582,000	+120,000
Benefits for former personnel (13.0).....	25,000	25,000	--
Travel (21.0).....	1,269,000	1,284,000	+15,000
Transportation of things (22.0).....	185,000	160,000	-25,000
Rental payments to Others (23.2).....	610,000	610,000	--
Communications, Utilities, and Miscellaneous Charges (23.3).....	4,842,000	5,542,000	+700,000
Printing and reproduction (24.0).....	821,000	775,000	-46,000
Consulting services (25.1).....	151,000	153,000	+2,000
Other Services (25.2).....	13,591,000	13,298,000	-293,000
Purchases from Govt. Accts (25.3).....	4,970,000	4,859,000	-111,000
Supplies and materials (26.0).....	<u>7,816,000</u>	<u>7,358,000</u>	<u>-458,000</u>
Total.....	76,811,000	77,517,000	+706,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

National Toxicology Program - ...The House in its report 104-209, page 70 states that it remains concerned about the number of carcinogenicity tests being initiated under the National Toxicology Program (NTP) at NIEHS. The Committee requests a report prior to the fiscal year 1997 hearings on the number of chemicals tested or in the process of being tested each year. This should include the number of new chemicals for which full testing was initiated each year using the standard two year design model. The Director should be prepared to discuss this issue when he appears before the Committee next year.

Action Taken or to be Taken

The NIEHS report on the number of chemicals being tested by the NTP is currently under development and will be submitted to the Committee prior to the 1997 hearings.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Authorizing Legislation

PHS Act Other Citation	U S Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Budget Estimate
Research and Investigation					
Section 301	42§241	Indefinite	> \$271,883,000	Indefinite	> \$277,909,000
National Institute of Environmental Health Sciences					
				Such sums as necessary	
Section 463	42§285	Such sums as necessary		Such sums as necessary	
National Research Service Awards					
Section 487 (d)	42§288	Such sums as necessary	10,964,000	Authorization is pending	11,205,000
Total, Budget Authority			\$282,847,000		\$289,114,000

NATIONAL INSTITUTES OF HEALTH

National Institutes of Environmental Health Sciences

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
		2/		
1988	198,431,000	225,724,000	220,709,000	215,666,000 5/
	3/	4/		
1989	218,471,000	216,985,000	223,168,000	223,454,000 7/
	6/			
1990	226,471,000	232,479,000	234,048,000	232,476,000
1990	Sequester			-3,242,000 9/
		8/		
1991	235,792,000	244,832,000	242,765,000	241,028,000 10/
1992	254,484,000	254,912,000	250,873,000	251,575,000 11/
1993	261,513,000	252,564,000	255,115,000	251,187,000
1994	261,306,000	264,249,000	264,249,000	264,249,000
	12/			13/
1995	267,955,000	266,400,000	267,955,000	266,988,000
1995	Rescission			-422,000
	12/	14/	12/	14/
1996	278,832,000	288,898,000	275,861,000	288,898,000
	12/			
1997	289,114,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ The 1989 request excludes funding for AIDS research and education (\$4,234,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Excludes \$9,183,000 in NRSA training programs not considered.

5/ Excludes enacted administrative reduction of \$2,714,000.

- 6/ The 1990 request excludes funds for the National HIV program (\$4,377,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
- 7/ Excludes enacted administrative reduction of \$788,000.
- 8/ Excludes \$10,586,000 in NRSA training programs not considered
- 9/ Excludes enacted administrative reduction of \$8,064,000
- 10/ Excludes enacted administrative reductions of \$4,871,000 and \$456,000.
Includes \$3,000,000 real transfer from the National Cancer Institute
- 11/ Excludes enacted administrative reduction of \$3,928,000.
- 12/ Excludes funds for HIV research activities consolidated in the Office of AIDS Research.
- 13/ Excludes enacted administrative reductions of \$578,000
- 14/ Includes funds for HIV research activities

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	70	70	70
Division of Intramural Research.....	395	415	415
Division of Extramural Research and Training.....	49	48	48
Office of Management.....	140	138	138
Total, NIEHS.....	654	671	671

Average GS/GM Grade

1992.....	10.13
1993.....	10.30
1994.....	10.44
1995.....	10.69
1996.....	10.69
1997.....	10.69

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

National Institute of Environmental Health Sciences

Program Administration

Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
ES-5.....	2	3	3
ES-4.....	5	5	7
Subtotal.....	7	8	10
Total - ES Salary.....	\$788,527	\$1,127,134	\$1,127,134
GS/GM-15.....	39	40	40
GS/GM-14.....	50	52	52
GS/GM-13.....	64	67	67
GS-12.....	63	66	66
GS-11.....	97	100	100
GS-10.....	2	2	2
GS-9.....	57	57	57
GS-8.....	23	23	23
GS-7.....	67	68	68
GS-6.....	25	25	25
GS-5.....	16	16	16
GS-4.....	34	37	37
GS-3.....	23	23	23
GS-2.....	2	2	2
Subtotal.....	562	578	578
Director Grade.....	6	6	6
Senior Grade.....	8	8	8
Full Grade.....	--	1	1
Subtotal.....	14	15	15
Ungraded.....	102	104	104
Total permanent positions.....	529	546	546
Total positions, end of year.....	685	707	707
Total full-time equivalent (FTE) employment, end of year.....	654	671	671
Average ES level.....	ES-4	ES-4	ES-4
Average ES salary.....	\$112,647	\$115,714	\$119,185
Average GS/GM grade.....	10.69	10.69	10.69
Average GS/GM salary.....	\$47,450	\$49,823	\$52,812



WEDNESDAY, APRIL 24, 1996.

NATIONAL CENTER FOR RESEARCH RESOURCES

WITNESSES

JUDITH L. VAITUKAITIS, M.D., DIRECTOR

LOUISE E. RAMM, Ph.D., DEPUTY DIRECTOR

ALBERT F. MARRA, Ed.D., EXECUTIVE OFFICER

ANNE E. SUMMERS, BUDGET OFFICER

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. Next we will hear from the National Center for Research Resources. We're pleased to welcome Dr. Judith Vaitukaitis, the director.

Dr. Vaitukaitis, welcome.

Dr. VAITUKAITIS. Thank you.

Mr. PORTER. Please introduce the people who are with you and then proceed.

INTRODUCTION OF WITNESSES

Dr. VAITUKAITIS. To my far left is Dr. Albert Marra, who is the executive officer; to my immediate left is Anne Summers, our budget officer; and to my right is Dr. Louise Ramm, who is our deputy director. Of course, you know Dr. Varmus and Mr. Williams.

Thank you.

OPENING STATEMENT

Mr. Chairman and members of the committee, I am pleased to appear before you today to discuss the programs of the National Center for Research Resources. NCRR creates, develops, and provides state-of-the-art research technologies, as well as specially-adapted research facilities for biomedical technology, animal-based and patient-oriented research.

Because infrastructure is highly sophisticated and costly, it makes sense that investigators share the vast array of tools and technologies they need to explore disease and its remedies. Resource sharing, in turn, leverages precious Federal research dollars. NCRR-supported research resources and other related activities collectively serve as a catalyst for discovery.

Shared research facilities promote collaborations across scientific disciplines and provide quick, flexible approaches to new and emerging research needs, in partnership with the other institutes and centers across the National Institutes of Health.

These research resource facilities host more than 10,000 investigators nationwide each year. Those investigators receive more

than \$1.3 billion in primary research support, almost 75 percent through research-initiated project grants from the other NIH components.

Sophisticated technologies such as high-field nuclear magnetic resonance, intermediate voltage electron microscopes, and synchrotrons have been critical to characterizing biologically important molecules and shedding light on the causes of disorders like Lou Gehrig's disease, AIDS, and brain disorders. NCCR supports a national network of biomedical technology centers that promote collaborations among the scientists around the country.

For example, NCI-supported investigators, in collaboration with NCCR-funded scientists operating the Metabolic NMR Research Resource at the University of Pennsylvania, developed a more reliable imaging approach that found that approximately 75 percent of breast biopsies of tumors that turn out to be benign can be avoided by using a combination of contrast media and high-resolution magnetic resonance imaging. The instrumentation is sensitive enough to distinguish benign tumors without sacrificing the capacity to detect cancers. With additional development, this approach may help reduce health care costs by eliminating unnecessary biopsies.

One way to share scarce resources is to distribute them widely through smart network-connected technologies, thereby creating virtual laboratories.

The NCCR supports a center in San Diego for intermediate voltage electron microscopy that allows investigators in other geographic areas long-distance access to a powerful microscope that is unavailable at most institutions. Investigators are able to ship tissue samples to San Diego, where the samples can be viewed and the three-dimensional images can be reconstructed remotely from a computer work station that controls the San Diego microscope via the Internet.

NCCR also supports a novel network of seven regional primate research centers and develops other shared resources that provide a broad range of research models of human disease.

For example, NCCR-supported investigators have successfully infected macaque monkeys with a new hybrid virus, called SHIV, which is a combination of parts of both the simian and human immunodeficiency viruses. Because the monkeys rapidly develop full-blown AIDS and the hybrid virus carries the outer part, or the envelope, of HIV-1, this model may provide another mechanism for developing and testing vaccines very quickly and may bring us one step closer to a vaccine against the human immunodeficiency virus, or HIV.

Clinical research translates knowledge gained in such pre-clinical studies to human patients. Equally important, insights gained through studies with patients can be carried back to the laboratory, where scientists can make major leaps in fundamental understanding of biological processes.

Often, specialized clinical, laboratory, and computer facilities, as well as highly-skilled staff, are required to conduct sophisticated clinical research. NCCR's nationwide network of about six dozen general clinical research centers, or GCRCs, each year allow more than 7,500 investigators to share the resources they need to con-

duct more than 5,000 patient-centered research studies across a broad spectrum of diseases.

For example, investigators at a GCRC developed an enhanced stress test that can help physicians detect latent heart disease. Thallium, a radioactive substance that can help image narrowed or blocked blood vessels, was injected into patients during a treadmill stress test. This thallium screening predicted coronary heart disease better than exercise electrocardiogram alone, particularly in high-risk, symptom-free individuals. The thallium stress test will allow physicians to detect potential blockages in blood vessels sooner and more easily than before, and to start treating heart disease before it causes heart attacks.

To better understand disease, investigators need a toolbox filled with sophisticated biomaterials, ranging from cells, genes, and tissues, to models of human disease. As more of the human genome is sequenced and specific gene abnormalities are identified, the demand for induced mutant animals, such as transgenics and knock-outs, will grow. In response to this need, NCCR now supports a shared national resource of stocks of newly-developed strains of genetically-altered mice for the biomedical community.

NCCR's shared instrumentation grant program underwrites the cost of state-of-the-art instruments, such as magnetic resonance imagers, electron microscopes, and cell sorters, located at research institutions with a high concentration of NIH-supported investigators. This logistical arrangement permits an average of 15 scientists to economically meet their needs for expensive instrumentation. Besides reducing the overall cost of research, this kind of sharing encourages investigators to collaborate across scientific disciplines and helps them increase their knowledge and develop new research techniques.

NCCR programs also enhance research environments at minority colleges and universities that award doctoral degrees in the health sciences. A new NCCR program, co-sponsored by NCCR and the NIH's Office of Research on Minority Health, will help minority institutions that do not award doctoral degrees to further develop their faculties and collaborate with graduate schools to ensure that adequate numbers of minority students continue in the career pipeline as graduate students. That need is self-evident. In 1993, fewer than 1 percent of earned Ph.D.s in the biological sciences went to African Americans and Hispanics.

Since 1980 NCCR has sponsored a program to attract minority high school students to careers in biomedical research and the health professions, giving thousands of students and science teachers hands-on experience in biomedical research laboratories each summer.

Another NCCR effort, the science education partnership awards program, spurs scientists to work with educators and other organizations to improve young students' and the public's understanding of science. One innovative project is CityLab, a biotechnology learning laboratory in Boston that provides teachers and young students access to state-of-the-art facilities and curricula otherwise unavailable to most school systems. This successful science education model is now being distributed throughout the country.

In conclusion, whether infrastructure is defined as technological, animal, clinical, or human, its shared use stimulates cost savings and provides opportunities for major medical discoveries and improved human health.

The task for NCRR, as a major custodian of shared scientific tools and technologies, is to keep up with the rapid pace of science and to continue to quickly adapt to current realities and future challenges.

Mr. Chairman, the fiscal year 1997 budget request for the National Center for Research Resources is \$309,344,000. I would be pleased to answer any questions you and your colleagues may have.

[The prepared statement and biography of Dr. Judith Vaitukaitis follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Center for Research Resources

Mr. Chairman and Members of the Committee:

I am pleased to appear before you today to discuss the programs of the National Center for Research Resources (NCRR). NCRR creates, develops, and provides state-of-the-art research technologies, specially adapted research facilities for biomedical technology, animal-based and patient-oriented research environments, along with an array of other human and research shared resources. Because this infrastructure is highly sophisticated and costly, it makes sense that investigators share the vast array of tools and technologies they need to explore disease and its remedies. Resource sharing, in turn, leverages precious Federal research dollars. NCRR-supported research resources and activities collectively serve as a "catalyst for discovery." Shared research facilities promote collaborations across scientific disciplines and provide quick, flexible approaches to new and emerging research needs in partnership with the other institutes and centers across the National Institutes of Health. NCRR-supported research resource facilities alone host more than 10,000 investigators nationwide each year.

Sophisticated technologies--such as high-field nuclear magnetic resonance, intermediate voltage electron microscopes, and synchrotrons--sources of high-energy X-rays to study molecules and atoms--have been critical to characterizing biologically important molecules and shedding light on the causes of disorders like Lou Gehrig's disease, AIDS, and brain disorders. NCRR supports a national network of biomedical technology centers that collaborate with scientists around the country. For example, NCI-supported investigators, in collaboration with NCRR-funded scientists operating the Metabolic NMR Research Resource at the University of Pennsylvania, developed a more reliable imaging approach and found that approximately 70 percent of breast biopsies of tumors that turn out to be benign can be avoided by using a combination of contrast media and high-resolution MRI analysis. The instrumentation is sensitive enough to distinguish benign tumors without sacrificing capacity to detect cancer. This approach may help reduce health care costs by eliminating unnecessary biopsies.

Another way to share scarce resources is to distribute them widely through "smart" network-connected technologies, thereby creating "virtual laboratories." The NCRR supports a center in San Diego for intermediate voltage electron microscopy that will allow investigators in other geographic areas to ship tissue samples to San Diego, where the samples can be viewed remotely from a computer workstation that controls the San Diego microscope via the Internet. Investigators can view samples in real time and reconstruct three-dimensional images of tissues by having microscopy data concurrently processed by the San Diego Supercomputer Center, which NCRR also helps support. This approach is being extended to other computer-intensive imaging and microscopy technologies and to other biotechnology-related resources that scientists use for structure-based drug design.

NCRR also supports a novel network of seven Regional Primate Research Centers and develops other shared resources that provide a broad range of research models, from non-human primates to invertebrates and non-animal models of disease. Investigators at Regional Primate Research Centers have recently discovered and characterized a simian model of human AIDS and found that an experimental antiviral drug known as PMPA completely protects macaque monkeys exposed to simian immunodeficiency virus (SIV), with no toxicity. This research suggests that PMPA could potentially prevent HIV infection in health care workers, newborns exposed during the birth process, and others accidentally exposed to the virus. In addition, investigators at the primate centers have successfully infected macaques with a hybrid virus, SHIV, a combination of parts of simian and human immunodeficiency viruses, to induce disease in the infected macaques. This new hybrid virus may prove important in developing a vaccine against human AIDS.

Other important work at these facilities includes stem cell research, which may lead to advances in a wide range of medical fields including organ transplantation and tissue repair as well as human gene therapy. Primate center researchers are also studying surfactant, a protein that is lacking in infants with respiratory distress syndrome. They have shown that a synthetic peptide containing surfactant is safe and effective for nonhuman primates, providing a basis for proceeding to clinical trials in human infants.

Clinical research translates knowledge gained in such pre-clinical studies to human patients. Equally important, insights gained through studies with patients can be carried back to the laboratory where scientists can make major leaps in fundamental understanding. However, sophisticated clinical research cannot be conducted in just any hospital or clinic. Often, specialized clinical, laboratory, and computer facilities, as well as highly skilled staff, are required. NCRR's nationwide network of about six dozen General Clinical Research Centers (GCRCs) each year allows more than 7,000 investigators to share the resources they need to conduct more than 5,000 patient-centered research studies. This network also provides an effective environment for training and junior career development in clinical research.

GCRCs are utilized for a broad range of research--from pilot projects to large-scale clinical trials--related to women's health, AIDS, heart disease, cancer, diabetes, osteoporosis, as well as neurodegenerative, behavioral, and rare diseases. For example, after a year of treatment and testing in one GCRC, investigators recently found that individuals who took a combination of antioxidants and low density lipoprotein (LDL)-lowering drugs attained significantly lower total cholesterol and LDL cholesterol levels. This therapy may help reduce the risk of heart attacks in people with high blood cholesterol levels and coronary artery disease, which is a leading cause of death for Americans.

Exercise electrocardiogram screening can help physicians detect heart disease, but researchers have now validated an even better thallium stress test, which employs a treadmill. More than 250 healthy siblings of patients with heart disease were brought to a General Clinical Research Center where they underwent a standard treadmill exercise electrocardiogram and were also injected with thallium, a radioactive substance that reveals narrow or blocked blood vessels. Thallium screening predicted coronary heart disease better than exercise electrocardiogram

alone, particularly in high-risk, symptom-free individuals. The thallium stress test will allow physicians to detect potential blockages in blood vessels sooner and more easily than before, and to start treating heart disease before it causes heart attacks.

Gene therapy, while still in its infancy, has the potential to correct an array of diseases that are caused by faulty genes. This year NCRR launched a resource-sharing program, in partnership with three NIH Institutes, to create a network of gene vector laboratories that will produce and distribute high-quality vectors to ferry potentially helpful genes into patients' cells. In FY 1997 this initiative will continue, and will also include studies of gene vectors in animal models.

To better understand disease, investigators need a toolbox filled with sophisticated biomaterials, ranging from cells, genes, and tissues, to models of human disease. As more of the human genome is sequenced and specific gene abnormalities are identified, the demand for induced mutant animals--transgenics and knockouts--will grow. NCRR supports a shared national resource of genetic stocks of animals for the biomedical community. The Jackson Laboratory validates, preserves, and distributes newly developed strains of genetically altered mice to investigators across the country.

NCRR's Shared Instrumentation Grant program underwrites the cost of state-of-the-art instruments, such as magnetic resonance imagers (MRIs), electron microscopes, and cell sorters, located at research institutions with a high concentration of NIH-supported investigators. This logistical arrangement permits an average of 15 scientists to economically meet their needs for instrumentation that costs \$100,000 to \$400,000 and more. Besides reducing the overall cost of research, this kind of sharing encourages investigators to collaborate across scientific disciplines, and helps them increase their knowledge and develop new research techniques.

NCRR programs also enhance research environments at minority colleges and universities that award doctoral degrees in the health sciences. A new NCRR program, co-sponsored by NCRR and NIH's Office of Research on Minority Health, will help minority institutions that do not award doctoral degrees to further develop their faculties and to ensure that adequate numbers of minority students continue in the career pipeline as graduate students. The need is self-evident: in 1993, fewer than one percent of earned PhDs in the biological sciences went to African Americans and Hispanics.

Since 1980 NCRR has sponsored a program to attract minority high school students to careers in biomedical research and the health professions. This gives thousands of students and science teachers hands-on experience in biomedical research laboratories each summer. Another NCRR effort, the Science Education Partnership Awards program, spurs scientists to work with educators and other organizations to improve students'--ranging from kindergarten through 12th grade--and the public's understanding of science and promotes interest in scientific and other health-related careers. One innovative project is CityLab, a biotechnology learning laboratory at Boston University School of Medicine. CityLab provides teachers and high school and middle school students access to state-of-the-art facilities and curricula otherwise unavailable to most school systems. This successful science education model has now been disseminated throughout

New England and to other parts of the country.

In conclusion, whether infrastructure is defined as technological, animal, clinical, or human, its shared use stimulates cost savings and provides opportunities for major medical discoveries that improve human health. The task for NCRR, as a major custodian of shared scientific tools and technologies, is to keep up with the rapid pace of science, and continue to quickly adapt to current realities and future challenges.

Mr. Chairman, the FY 1997 budget request for the National Center for Research Resources is \$309,344,000. I would be pleased to answer any questions you may have.

CURRICULUM VITAE

Judith L. Vaitukaitis, M.D.
 Director
 National Center for Research Resources
 National Institutes of Health

Birth place: Hartford, Connecticut

Education: B.S., Tufts University, 1962; M.D., Boston University School of Medicine, 1966; Internship and Residency, Second (Cornell) Medical Service, Bellevue Hospital, NY, NY, 1966-68; Medical Resident, University Hospital, Boston, MA, 1968-69; Academic Training Fellow, Boston University School of Medicine, 1968-71; Endocrine Section, National Cancer Institute, NIH, Bethesda, MD, 1970; Special PHS Postdoctoral Research Fellow, Reproduction Research Branch, NICHD, NIH, Bethesda, MD, 1971; Senior Staff Fellow, Reproduction Research Branch, NICHD, NIH, Bethesda, MD, 1971-73.

Professional History: 1993 to present, Director, National Center for Research Resources (NCRR), NIH; 92-93, Acting Director, NCRR, NIH; 91-93, Deputy Director for Extramural Research Resources, NCRR; 1986-1991, Associate Director for Clinical Research and Director, GCRC Program, NCRR; 1977-86, Professor of Medicine, Boston University School of Medicine (BUSM); 1980-86, Professor of Physiology, BUSM; 1974-86, Head, Section of Endocrinology and Metabolism, Boston City Hospital, Boston, MA.; 1975-86, Program Director, General Clinical Research Center, BUSM; 1977-80, Associate Professor of Obstetrics and Gynecology, BUSM; 1975-80, Associate Professor of Physiology, BUSM; 1974-77, Associate Professor of Medicine, BUSM; 1973-74, Senior Investigator, Reproduction Research Branch, NICHD, NIH, Bethesda, MD.

Societies and Associations: Association of American Physicians; American Society for Clinical Investigation; American Federation for Clinical Research; The Endocrine Society.

Honors and Awards: 1995, Presidential Meritorious Executive Rank Award; 1987-1989, Associate Editor, Yearbook of Endocrinology; 1984-1986, Editorial Board, Endocrine Research; 1979-84, Editorial Board, Endocrine Research Communications; 1978-87, Editorial Board, Proceedings of the Society for Experimental Biology and Medicine; 1977-1985, Editorial Board, Archives of Andrology; 1973-1980, Editorial Board, Journal of Clinical Endocrinology and Metabolism; Distinguished Alumna Award, Boston University School of Medicine; Mallinckrodt Award for Investigative Research, Clinical Radioassay Society; 1983-86, General Clinical Research Centers Committee (Study Section); 1979-80, Population Research Committee Study Section, NICHD; 1977-80, Scientific Advisory Committee, Program for Applied Research on Fertility Regulation, Aid to International Development; 1975-78, Breast Cancer Task Force, Epidemiology Subcommittee, National Cancer Institute; Alpha Omega Alpha; Begg (honor) Society.

Publications: Author of over 160 scientific papers with four selected as Citation Classics; editor of one book.

PRESIDENT'S BUDGET REQUEST

Mr. PORTER. Dr. Vaitukaitis, we were initially concerned to see a decrease in the President's request for your center compared to 1996, but is the cut almost entirely associated with the fact that the President does not request any funding for extramural facilities construction, which received \$20 million in 1996, and are your other programs protected from cuts for the most part?

Dr. VAITUKAITIS. If one normalizes our 1996 budget, removing the \$20 million that we have this fiscal year for construction, then our 1997 budget request would increase about 2 percent, in keeping with the increase for most of the other institutes and centers across NIH. Construction dropout is the major reason for the decrease.

Mr. PORTER. Apparently the President's budget also does not request any funds for the National Science Foundation facilities construction program. Does your budget and NSF's reflect the judgment that the backlog in facility construction at universities is being overcome, or is this simply a way to save money?

Dr. VAITUKAITIS. I think it reflects the priorities that we have for fiscal year 1997 in terms of replacing the clinical research center on the NIH campus, and, with the funds available, supporting primarily investigator-initiated research project grants.

Dr. VARMUS. The other point I would make, Mr. Porter, is that we have, of course, a large annual investment in construction, facilities, and maintenance through the indirect cost payments. We intend to restore extramural construction in 1998, all things being equal, but we are, of course, trying to mold the budget to allow us to build a clinical center without sacrificing research project grants.

IMPACT OF MANAGED CARE

Mr. PORTER. Yes. Can you quantify for us the monetary impact of managed care and lost third-party reimbursements in the general clinical research centers that your institute supports?

Dr. VAITUKAITIS. It's very hard to quantify. What is happening is that, in those areas of the country where managed care has penetrated very heavily, the demand for general clinical research centers resources has increased markedly. The overall census of the host hospitals—in terms of patient admissions and number of patient days—has decreased markedly. The census for the GCRCs in terms of outpatient-based research and inpatient research days had stayed level, and now it's increasing. In fact, we're receiving calls and letters quite often from GCRC program directors who are operating the GCRCs requesting more support than we can give—we are very limited in what we can supply.

Over the last couple of years we have moved more toward cost-effective outpatient-based research to try to overcome the cost impact of managed care.

The impact of managed care on third-party reimbursements is real, but it's difficult to measure specifically because of an uneven pattern across the country in terms of the impact.

Our third-party reimbursements from fiscal year 1994 dropped by about \$1.5 million to \$2 million, which would have paid for one freestanding center.

We're concerned that this pattern may continue over the next several years.

Mr. PORTER. Is there any Federal or State policy requiring managed care or health insurance companies to pay the reasonable costs of basic clinical care associated with the clinical research projects?

Dr. VAITUKAITIS. I am unaware of anything that is in place currently.

Until a couple of years ago, many managed care organizations or third-party carriers would pick up the normal patient care costs associated with a patient having to be hospitalized or having to be seen in an office or an outpatient study area.

Patients sign consent forms to participate in a phase one or phase two clinical trial, even though the patients have to be hospitalized because of their underlying illness. Third party providers or managed care organizations are almost routinely refusing to pay for those patients' routine patient care coverage, and that's a departure from what went on previously. It was a problem before, but now it's been magnified.

Mr. PORTER. Mrs. Lowey?

IMPACT OF MANAGED CARE

Mrs. LOWEY. Thank you, Mr. Chairman.

I welcome you, Dr. Vaitukaitis.

Following up on Mr. Porter's question, the area I represent, New York, is home to some of the Nation's best teaching hospitals and academic medical centers. And, as you know, these fine institutions in New York and elsewhere participate heavily in NIH's extramural research grants.

There is concern that, in the face of the dramatic increase of managed care, coupled with Federal budget cuts, our teaching hospitals are having a more difficult time maintaining their focus on research.

You recently presented your analysis of this problem at a meeting of the advisory group on the inclusion guidelines, which was organized by Dr. Pinn and the Office of Research on Women's Health. Can you briefly share with us your analysis of the current problems faced by teaching hospitals and your suggestions about what you believe NIH can do to assist these institutions so that they can continue to perform their role as centers for research activity?

Dr. VAITUKAITIS. Thank you. That's a rather complex question.

The study that I presented was a pilot study that was carried out by Lewin-VHI to assess the impact of managed care on clinical research. Seven institutions were examined as case studies at the University of Pennsylvania; Johns Hopkins; University of Washington/Seattle; Oregon Health Sciences University in Portland, Oregon; University of California, San Francisco; Stanford; and the University of Minnesota.

First of all, Lewin-VHI talked with the high-level administrators at the university hospitals, they talked with high-level managers in managed care organizations, and they talked with clinical investigators. All those institutions have general clinical research centers.

What they found frequently was a disconnect—the high-level managed care officers would state that they supported clinical research, but yet, in practice, they were not. In fact, the general consensus was that managed care organizations did not think that it was their role to support clinical research; they saw research as a public good; that it should be funded Federally or at least funded elsewhere.

Of the institutions that I enumerated, four of the seven have had marked impact of managed care, and their patient census has decreased. Their recoveries from delivering health care have markedly impacted their clinical care income and it's rapidly decreasing. Those extra funds are usually shared with the dean of the medical schools, as well as department heads, to support young investigators to give them a jump start on their careers.

What's happening is that now the funds aren't available to help support those young people. The other thing that compounds the problem is that there is more demand on their time to see patients to generate income. So they're in a catch 22.

We are in the process of trying to come up with some ways to protect young clinical investigators, especially young M.D.s, for the critical interface between basic and clinical research or patient-oriented research.

One of the logical suggestions of the Lewin report is to work with managed care organizations to try to enhance access to patients. There are some managed care organizations that are very well organized, especially the not-for-profit ones, which actually have NIH funding to carry out clinical trials; they do this very effectively. They have very strong informatics systems, better than most academic health centers have, and so it would be logical to work closely with them to carry out more effective and probably more cost-effective clinical trials, especially phase three clinical trials, and some forms of outcomes research.

But they are not interested in understanding the basic causes of disease. They're not interested in carrying out phase one and phase two clinical trials, because they see that as a burden to them financially, making them less competitive with other managed care organizations. They would have to charge more to cover those costs, even though there would be cost-sharing from the National Institutes of Health or some other organizations to help support clinical research.

The impact so far has been limited, but it's changing very rapidly. In fact, the Lewin report was completed about eight months ago, and since that time the progress of managed care is rapidly advancing. It's like standing in shifting sands.

Dr. VARMUS. Perhaps I could add one encouraging note, Mrs. Lowey.

Mr. Porter asked me a few days ago whether other agencies were discussing with us a plan similar to the plan that has been worked out between the NCI and the Department of Defense. As a result of conversations among me, Claude Lenfant of the Heart, Lung, and Blood Institute, and Dr. Bruce Vladeck, the administrator of the Health Care Financing Administration, the Department will be announcing today Medicare is going to support a clinical trial of

pulmonary reduction surgery for chronic obstructive pulmonary disease.

This is a very important development, and you'll be hearing about it from the Department in the course of the next 24 hours.

IMPACT OF MANAGED CARE

Mrs. LOWEY. I just wonder, as a follow-up question, are there any other suggestions you have? I mean, are we going to depend on the good nature of the HMOs, obviously, they are there to make a profit. Will NIH pick up this responsibility for clinical research?

Dr. VARMUS. We have more examples. In addition, Dr. Nathan's clinical research panel, which is advising me on these issues is meeting actively, trying to convince the managed care providers and insurers that, in the long run, there is a tremendous advantage to supporting clinical trials. In the long run clinical research is going to be required to have effective, efficient, and cost-advantageous care.

Dr. VAITUKAITIS. There are a couple of examples of very creative solutions that are being entertained and being developed at some of the academic health centers.

For instance, the Fox Chase Cancer Center at the University of Pennsylvania has developed an outreach program to suburban hospitals. The Fox Chase staff go out to the HMO-related hospitals and serve on the patient care teams to identify patients who would be eligible to participate in cancer research clinical trials and bring them back to the University of Pennsylvania facilities. So it is a two-way street.

At the University of California, San Francisco, they have developed an outreach program with their house staff going to Kaiser Permanente facilities, and working with some of the investigators to identify potential patients to participate in clinical research projects.

There is a move afoot, but it's not universal—it's customized at each institution at this point.

Mr. PORTER. Thank you, Mrs. Lowey.

Mr. Miller?

Mr. MILLER. No questions.

Mr. PORTER. Mr. Stokes?

EXTRAMURAL FACILITIES CONSTRUCTION

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Vaitukaitis, under the extramural facilities construction program, 25 percent of appropriated funds are clearly directed to what's called "institutions of emerging excellence." These institutions are described in legislation as institutions receiving grants under the Research Centers in Minority Institutions and the minority Centers of Excellence programs.

Can you tell us how many applications you received from minority institutions for the fiscal year 1995 grant cycle?

Dr. VAITUKAITIS. Yes. In fiscal year 1995 we received a total of 88 applications. Seven were from centers of excellence. These are 25 eligible institutions who receive awards from the Bureau of Health Professions, a part of the Health Resources and Services Administration. In addition, we also received five applications from

the regional primate research centers, which is another set-aside for the extramural construction authority.

In 1995 we made seven awards. None were made to centers of excellence. One would have been made to a center of excellence, but, unfortunately, that institution had already competitively bid and had awarded a contract for construction at the facility for which they requested funds.

Mr. STOKES. The bottom line is none were made to minority institutions?

Dr. VAITUKAITIS. Right. That's correct.

Mr. STOKES. Tell us why.

Dr. VAITUKAITIS. In fiscal year 1995 we were initially appropriated \$20 million for the construction program, of which \$10 million was rescinded. The NIH Revitalization Act of 1993 stipulates, under section 481 A and B, that awards are to be made competitively based on scientific merit.

The next eligible institution that was a center of excellence was significantly down the pay list, and we could not reach it with the \$10 million.

There were a total of seven applications, as I've stated. Four were deemed non-competitive by the Review Committee, so there were three institutions that were eligible. One would have been funded last year if it had not already bid and awarded the contract. We worked with that institution considerably to see if they could step out that part of the project and rebid, but the penalty cost would not make it cost-effective to do that. We mutually decided it would be better to make an award to another eligible institution on the list.

Mr. STOKES. Were there any representatives from minority institutions on the peer review plan reviewing these proposals?

Dr. VAITUKAITIS. Yes, there were several.

Mr. STOKES. Several?

Dr. VAITUKAITIS. Several. Yes.

Mr. STOKES. Can you put a list of them into the record for us?

Dr. VAITUKAITIS. We certainly can.

Mr. STOKES. Thank you.

[The information follows:]

The following representatives from minority institutions participated in the meeting of the Scientific and Technical Review Board, reviewing the applications for the FY 1995 extramural construction program:

John R. Aldrete, Ph.D., University of Texas Health Science Center, San Antonio, TX.

Aureo F. Andino, B. Arch., University of Puerto Rico, Rio Piedras, PR.

Mohamed A. Bayorh, Ph.D., Morehouse School of Medicine, Atlanta, GA.

In addition to the above, the following minorities were members of the review board.

Philip Artin, M.Sc., The Urban Development Group, Washington, DC.

Zang He Cho, Ph.D., University of California, Irvine, CA.

Angel G. Jordan, Ph.D., Carnegie Mellon University, Pittsburgh, PA.

Nathaniel Pitts, Ph.D., National Science Foundation, Washington, DC.

EXTRAMURAL FACILITIES CONSTRUCTION

Mr. STOKES. The term "institutions of emerging excellence" is a recognition by the Congress that all institutions are not competing from a level playing field. Further, while these emerging institutions have lagged behind in their facility development, they have

a great deal to contribute, and should not be penalized because of their relatively recent emerging capabilities. In fact, the 25 percent statutory designation was established to ensure that these institutions were able to successfully secure annual facility construction funds.

To meet the clear legislative intent of this 25 percent designation, does the NCRR have a specific plan that would help facilitate this direction?

Dr. VAITUKAITIS. Yes. We've had this program since 1994, and when the request for applications is published, we contact each eligible center of excellence institution to apprise them of the availability of this program and the funds set-aside for that cohort of institutions.

We have just received the applications for the fiscal year 1996 cohort last Friday. So far we have 74 applications, 14 of which are from centers of excellence institutions. That's the largest number we've received to date.

We've also encouraged those institutions to meet with our staff to coach them in terms of how to address the problems with their applications. We hope that would work.

In the previous year, 1994, the first year we had this program, there were eight applications from centers of excellence for the \$7 million that were available. There were 69 applications, and we made 8 awards. Two of those awards were to centers of excellence—to Meharry Medical School and to Morehouse.

Mr. STOKES. According to the Congressional Budget Justification, Doctor, no funds are requested for the extramural facilities construction program in fiscal year 1997; is that correct?

Dr. VAITUKAITIS. That's correct.

Mr. STOKES. And, so, you're proposing the elimination of the program?

Dr. VAITUKAITIS. In fiscal year 1997, the highest priorities for the budget are to help build a replacement clinical research center on the NIH campus and to keep as many investigators supported as possible through investigator-initiated research project grants.

As Dr. Varmus stated earlier, it's hoped that we'll be able to reinstate funds for the construction program with the fiscal year 1998 budget.

Mr. STOKES. Was this based upon some evaluation and study that was made?

Dr. VAITUKAITIS. Not to my knowledge.

Dr. VARMUS. It was based—

Mr. STOKES. Dr. Varmus, do you want to respond?

Dr. VARMUS. Yes. I'd like to. It was based on our concern for sustaining our highest priority initiatives in 1997, given the constraint of spending a considerable amount of money to construct the clinical research center, an enterprise which needs to be done. We propose funding the center in a single year, placing severe demands on other parts of our budget because of the overall constraints on the Federal budget this year.

We have tried to conserve our funds, by holding programs to minimum increases or holding them steady for this fiscal year, to keep our success rates and numbers of new grants as high as possible. We fully intend to resume the program in 1998.

Mr. STOKES. Thank you, Mr. Chairman.

PRIMATE RESEARCH CENTERS

Mr. PORTER. Thank you, Mr. Stokes.

Last year an issue was raised about whether the primate center grants are truly competitively awarded. It's my understanding that the same centers have received awards for over 30 years, and that none have been discontinued. Can you describe for us the process used to award the primate center grants and the criteria you used to extend continuation grants?

Dr. VAITUKAITIS. The seven regional primate research centers have been in place for more than 30 years. Each center initially was awarded funds to buy land and provide physical facilities—the buildings and the holding facilities for the non-human primates that are at the centers.

Each center is reviewed by an ad hoc group of reviewers who have expertise to review the work of the investigators who are carrying out research at those centers and also how the administration of each center is conducted.

Each investigator's project is individually scored and the level of NIH support to investigators is carefully evaluated.

It is unrealistic to close one of these centers down and then open up a new one somewhere. There is only one other place in this country where a facility exists that could possibly qualify as a regional primate center.

To start up a regional primate center in the current climate would cost, at a minimum, \$50 million and would require recruiting a cohort of investigators who have the requisite expertise for working with non-human primates.

The number of investigators working with non-human primates over the last several years has been steadily decreasing because of the impact of animal rights groups and the high cost of doing research with non-human primates.

The combination of all these factors means that these centers are awarded competitively, but non-competitively, if you will. They're thought of more as national laboratories for non-human primates that are distributed around the country to work closely with investigators from other institutions near and far.

ANIMAL CARE GUIDELINES

Mr. PORTER. I understand that the National Research Council has recently issued revised animal care guidelines. Do you plan to revise the Department's animal care guidelines to conform to these new standards?

Dr. VAITUKAITIS. The Institute for Laboratory Animal Research, a part of the National Academy of Sciences, has recently finalized and published the updated guide, which contains new performance-based caging requirements for animals which are more realistic in view of the current climate.

It is my understanding that that guide becomes the standard for the Public Health Service.

There are some disparities with the published Animal Welfare Act and title 9, subpart A, which is the implementation of the Animal Welfare Act.

The U.S. Department of Agriculture is the purveyor, if you will, of the Animal Welfare Act and title 9, subpart A, so it's really up to the Secretary of the Department of Agriculture to modify those laws, but I'm quite sure there will be input from other departments, which I think is critical.

Perhaps Dr. Varmus would like to make a comment.
Dr. VARMUS. No.

REAL-TIME MRI IMAGING

Mr. PORTER. Your budget justification describes how real time MRI imaging can now be done on the worldwide web with browser software. Will this bring the most advanced medical technology to rural areas, or will equipment costs still put it beyond the reach of most communities?

Dr. VAITUKAITIS. The cost of MRI is really the problem, but with the MRI becoming a more and more important and useful clinical tool, MRIs could undoubtedly be adapted for specific purposes, and work with the software that's available elsewhere through the Internet through browser access. It would help contain that cost, if MRIs were regionally placed, instead of being placed at every hospital. It would make more sense and be a cost-effective way to bring state-of-the-art technology to rural institutions.

TRANSGENIC ANIMAL MODELS

Mr. PORTER. It seems as if the scientific use of transgenic and knockout animals has exploded in the past several years. Is the supply of these animals keeping up with scientific demand? Second, does the present system of distributing these strains of animals need to be reviewed for efficiency and the diversity of its offerings?

Dr. VAITUKAITIS. You're quite correct that there has been an explosion of use of transgenics and knockouts for setting gene function, etc. The number of transgenics and knockouts that are out there are literally in the thousands. Some are really unique in that they are only of interest to a few investigators.

For those transgenics and knockouts that are of more widely-based interest, we have a center that we support at Jackson Laboratories that will validate the transgenic or **knockout** and make sure it's germ free and then make it available to investigators on an international basis, although it's predominantly for investigators in this country.

The big problem with transgenics and knockouts is locally at the institution. The animal care cost for investigators has skyrocketed, so a modification of the guide for animal care and use will help immensely with developing performance-based caging.

What currently goes on is that a very large cage holds several animals that huddle together in a small corner of that cage, and the cage size helps drive up the cost of laboratory animal facilities.

With performance-based caging based on **scientific** determinations, the animal care cost should be contained considerably and help investigators locally at their institutions.

The animal models of human disease are unparalleled currently because of all the technology—genetic technology—that's available. We've had to literally double the size of Jackson Laboratory over a period of two years because of the increase in terms of importing

transgenic and knockouts. They currently can bring in 100 new transgenics or knockouts annually. It's very time-consuming to work up these animals and put them in a production facility to make them available across the country.

Mr. PORTER. Mr. Miller, any final questions?

Mr. MILLER. No, Mr. Chairman.

Mr. PORTER. Mr. Stokes?

Mr. STOKES. Yes, I have few remaining questions

Mr. PORTER. Mr. Stokes.

EXTRAMURAL FACILITIES CONSTRUCTION

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Vaitukaitis, let me go back for a moment to our discussion about the extramural facilities construction program.

On page 143 of your justifications you make the statement, under the "research facilities," section that—"No funds are requested for this program in fiscal year 1997, reflecting the higher NIH priority for research project grants."

In light of the interest that this subcommittee has in this area of the budget, and in light of the language it has put into the law relative to the institutions of emerging excellence, and so forth, did you feel any obligation to notify this subcommittee of this higher priority which you established?

Dr. VAITUKAITIS. The budget priority reflects the President's budget request, and I understand that that does not require notifying anyone.

Mr. STOKES. Dr. Varmus, do you want to respond to my question?

Dr. VARMUS. My understanding is that's the usual protocol, but I think in this case, Mr. Stokes, it would have been sensible for us to have consulted with you about it.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. STOKES. I would think that that would have been appropriate in this case, also.

Doctor, let me ask you this: how long have the research centers in minority institutions now been in operation?

Dr. VAITUKAITIS. Since 1985.

Mr. STOKES. And, they were instituted through this subcommittee at that time, right. Tell us, what are some of the major activities underway at these institutions?

Dr. VAITUKAITIS. Some of the activities of the institutions—it varies considerably, because investigators have different interests.

For instance, at Meharry Medical College the RCMI program supports predominantly a neuroscience department which has been very productive in competing successfully for NIH grants.

In addition, it has helped develop graduate students who are among the first minorities to earn Ph.D.'s in neuroscience, which I think is a giant step forward.

At Morehouse Medical College, the RCMI program supports the development of a molecular biology department, and that department is moving forward very nicely, analogous to what's happening at Meharry.

At the University of Hawaii, investigators are working with a model, trying to understand why premature births are so much more common among minorities—African-Americans, Asian Pacific Islanders, and Asians. They have found that a substance thought to be a hormone, relaxin, actually is present in increased concentrations in the placental membrane among African-Americans and Asian Pacific Islanders and correlates directly with the increased risk for premature delivery.

If we can further develop and understand that, we should be able to develop a way to interfere with the relaxin that may induce premature births among those subsets.

Mr. STOKES. I would appreciate it if you would expand upon this question in the record.

Dr. VAITUKAITIS. Sure.

Mr. STOKES. So that we'll have a clear understanding of what these institutions have been doing and of the progress that they have made, also include in the record the history of funding for this particular program, if you would.

Dr. VAITUKAITIS. Sure.

[The information follows:]

Some major activities underway in RCMI institutions are as follows:

Charles R. Drew University of Medicine and Science

- Studies on the structure and function of surfactant proteins using synthetic peptides
- Molecular genetic studies to identify the mechanism of salt-sensitive hypertension in African Americans
- Prospective studies of cardiodynamic indicators of pregnancy hypertension
- Role of intracellular calcium in blood pressure elevation

City College, City University of New York

- Studies to understand the molecular events involved in organismal development
- Phylogenetic and antigenic variation in African HIV-1 isolates
- Synthesis of anti-HIV compounds

Clark Atlanta University

- Interaction of lead and mercury with DNA
- Identification of genetic determinants for bioflocculent production
- Effect of chlordane exposure on immune cell function
- Development of in vitro biomarkers for health risk assessment of exposure to toxic heavy metals

Florida A&M University

- Synthesis of potent and safe anti-inflammatory steroids
- Colchicine and taxol analogs as anti-cancer agents
- Development and evaluation of novel drug delivery systems including liposomes and transdermal patches
- Development of pharmacogenetic model with sensitivity for barbiturates

Howard University

- Molecular characterization of HLA-DR and -DQ genotypes associated with vitiligo
- Molecular genetic analysis of asthma
- Protocol standardization for PCR amplification of genomic DNA for oligonucleotide probe typing

Hunter College, City University of New York

- Effects of electromagnetic forces on genes involved in regulatory pathways
- Design and synthesis of anti-HIV and antibiotic drugs for AIDS and related infections
- Role of excitatory amino acids on neuropeptide regulation

Meharry Medical College

- Neurobiological basis of drug dependency and anxiety
- Projects in AIDS education and behavior modification
- Molecular mechanisms of erythropoietin during growth and differentiation

Morehouse School of Medicine

- Multidrug resistant phenotype of mammalian cells exposed to antiviral drugs
- Role of nucleoside transport in cardiovascular function
- Reactivity of molecularly defined mycobacterial antigens

Ponce School of Medicine

- Studies on allergen reactivity in an asthmatic population
- PCR diagnosis of perinatal HIV infection
- New flow cytometric method for analyzing CD8 cell function in HIV infected individuals

Tennessee State University

- Role of histamine release in regulation of cardiovascular function in hypertensive rats
- Comparison of cardiovascular reactivity and psychosocial effects in blacks and whites from stressors in laboratory and natural settings
- Effect of non-ionizing and ultraviolet radiation stress on cultured mammalian cell lines

Texas Southern University

- Amine oxidases and vascular injury in diabetes
- Molecular regulation and expression of signals affecting peripheral vascular resistance in salt-dependent hypertension
- Information base assessment and effect of instructional intervention on risk reduction of HIV transmission among minority populations

Southern University, Baton Rouge

- Synthesis of sulfonylpropenylamines for testing as cross-linkers for hemoglobin and oxyhemoglobin
- Molecular studies of a natural viral protease inhibitor
- Uterine metabolism and body temperature rhythm during decidualized pseudopregnancy

Tuskegee University

- Caprine arthritis encephalitis virus model for studying immunodeficiency diseases
- Computational modeling of the epidemiology of AIDS in humans
- Murine acquired immunodeficiency syndrome model for AIDS research

Universidad Central del Caribe

- Molecular biology studies on acetylcholine receptor using conotoxin analogues
- Neuropeptide Y and norepinephrine modulation of synaptic transmission
- Studies on natural history of AIDS

University of Hawaii

- Structure and expression of the gene encoding growth regulatory neuropeptides in crustaceans
- Collection of data on the distribution of risk factors for cardiovascular disease in Native Hawaiians

- Relaxin receptor: characterization, cloning and expression in human tissues and cells and role in premature birth

University of Puerto Rico, Medical Sciences Campus

- Studies on comparative neurobiology and biophysics
- Expression of tumor suppressor genes in mammalian cell lines
- DNA fingerprinting of Mycobacterium tuberculosis among TB patients with and without HIV infection

University of Puerto Rico, Rio Piedras

- Establishment and use of biological models to screen for anti-infective, antitumor and neurotoxic activity
- Molecular characterization of the synthesis of fibroin by spider glands
- Cellular and biochemical events involved in transdifferentiation in newt ocular tissue

University of Texas, El Paso

- Rattlesnake protease effects on blood coagulation and complement fixation
- Effect of alcoholic diets on rat hepatocytes
- Function of molecular chaperones in membrane assembly

Xavier University of Louisiana

- Psychosocial and behavioral aspects of prescription drug use in the Black elderly
- Studies on the pharmacodynamic implication of stress in experimental hypertension
- Use of radiotelemetry to quantitate behavioral problems in cholesterol-deficient rats

RESEARCH CENTERS IN MINORITY INSTITUTIONS
FUNDING HISTORY

YEAR	NUMBER OF GRANTS	AMOUNT
1985 Actual	7	\$4,771,000
1986 Actual	15	\$9,799,000
1987 Actual	15	\$10,000,000
1988 Actual	17	\$11,010,000
1989 Actual	17	\$15,312,000
1990 Actual	17	\$17,378,000
1991 Actual	17	\$21,950,000
1992 Actual	18	\$23,472,000
1993 Actual	18	\$23,362,000
1994 Actual	19	\$23,810,000
1995 Actual	17	\$24,142,000
1996 Estimate	19	\$26,363,000
1997 Estimate	19	\$26,363,000

FACILITIES' INFRASTRUCTURE

Mr. STOKES. As the director of the Nation's National Center for Research Resources, in your professional judgment, what is the state of the facilities' infrastructure at institutions of emerging excellence?

Dr. VAITUKAITIS. We talked specifically about the subset of institutions of emerging excellence because they are institutions that are eligible—like Stanford, University of Washington. I think your interests are predominantly minority institutions that have—

Mr. STOKES. Right.

Dr. VAITUKAITIS. Based on the study that was carried out by the National Science Foundation and recently published, historically black colleges and universities have a real facility need. They have a real problem getting funds from the private sector or from other sources to build new facilities, and their facilities need, where research is ongoing, is severe.

Mr. STOKES. And then a final question. In your professional judgment, what prevents them from competing on a level field for research project grants?

Dr. VAITUKAITIS. I think that's our fault. We need to have them compete—develop mechanisms for them to compete more effectively in a defined way so they get used to the way that other institutions and other investigators compete.

If we coach them better, I think they can do better. To get young investigators and protect them from other duties, from committee work, from heavy doses of patient care interactions, and mentor them well, I think we can do better.

Mr. STOKES. Thank you very much, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Vaitukaitis, we appreciate the fine job you're doing at the National Center for Research Resources, and we appreciate very much your excellent testimony this afternoon.

Dr. VAITUKAITIS. Thank you.

Mr. PORTER. Thank you.

[The following questions were submitted to be answered for the record:]

CLINICAL RESEARCH

Mr. Porter: How many research beds do the clinical research centers have nationwide, and what share of all research beds, both government and private, does that comprise?

Dr. Vaitukaitis: The GCRC program does not support a specific number of research beds. Some GCRCs are funded with a "discrete" configuration with a fixed number of beds supported, if that funding approach is cost-effective. Other centers are funded by the "per diem" method, which pays for actual number of research bed days used. At some GCRC sites both methods may be used to accommodate off-site (scatter beds) for clinical research in specialized units such as a neonatal intensive care unit, a coronary intensive care unit, or a psychiatric unit. As a result, the GCRC program specifies research days and visits in awards to its network of centers.

In "discrete" centers, occupancy is kept high by admitting category B, C, and D patients which provide "service patient credits", which in turn decrease the cost of operating those centers. Through these mechanisms, the GCRCs have been cost effective, with efficient utilization of not only the beds, but also GCRC-supported paramedical personnel. The utilization of each GCRC is closely monitored by NCRR staff and the approved level of research bed days is issued each year based on previous and anticipated utilization.

In FY 1994, there were 77,956 inpatient research days. There were an additional 5,542 inpatient scatter bed research days. The average length of stay for an inpatient on a GCRC was 3.6 days. In addition to inpatient research days, there were 245,016 outpatient research visits. The GCRC program provides inpatient research days and outpatient visits for investigators at Veterans Administration sites in San Diego, California and San Antonio, Texas.

The NIH Clinical Research Center (NCRC) is another major source of Federally-supported inpatient and outpatient research. In FY 1994, the NCRC hosted 72,167 research days and 73,353 outpatient research visits. The average length of stay in FY 1994 at the NCRC was 9-10 days.

Other Federally supported clinical research facilities include NASA's Ames Laboratory where about 10 beds have been supported; it is our understanding that that 10-bed facility is to be phased out. The USDA supports inpatient and outpatient studies for normal controls at its Nutrition Centers. The number of beds is relatively small. Pharmaceutical companies and private clinical trials study units have testing facilities but there is no known summary of that research capacity. On a limited basis, some academic health centers support clinical research facilities for inpatient and outpatient studies in anticipation of submitting a grant application for a clinical research center; that research capacity is unknown, but undoubtedly limited.

PRIMATE RESEARCH CENTERS

Mr. Porter: We have heard complaints that some primate centers are apparently not responsive to the requests from scientists not affiliated with the centers to use primate center animals in research projects. In fact, this concern was mentioned in the Levine panel review of the NIH AIDS program. What guidance does your Institute give the primate centers in setting priorities for allocating the use of their animals?

Dr. Vaitukaitis: The seven Regional Primate Research Centers (RPRCs) are readily accessible to local, regional, national and international biomedical and biobehavioral scientists who wish to use nonhuman primates in their research endeavors. In fact, more than 1,200 scientists conducted research projects at the RPRCs in FY 1995. Each RPRC has standardized procedures and criteria for evaluating each proposed research project. These include (a) the nature and scope of the research; (b) scientific merit, peer-reviewed and funded status; (c) availability of Center resources, e.g., animals, animal-housing, laboratory space and other support; (d) relevance to the Center's research mission; and (e) special requirements, such as biosafety facilities. If these criteria are satisfied, then the research project is approved and proceeds. I have heard this allegation for three years and have asked individuals who raised this issue to provide me with the name of the investigator so that he/she would be accommodated. No cases have been identified, but there certainly is the perception that there is an access problem.

The NCRR directs the RPRCs to give top priority to those research projects supported by NIH research grants. AIDS research, for example, has become a major priority at nearly all of the RPRCs, but research on neurological diseases, cardiovascular diseases, and other infectious diseases using nonhuman primates is also stressed. In other words, research at RPRCs is geared to address the overall mission of NIH and problems related to human health.

NATIONAL GENE VECTOR LABORATORIES

Mr. Porter: Your Center, along with three other Institutes, is supporting three national gene vector laboratories, which will develop vectors such as viruses and other agents that can transport new genes into human cells. We understand that the cost of vector production is very high and is a potential obstacle to gene therapy research. Why is that the case, and do you expect these national labs to develop less expensive vectors?

Dr. Vaitukaitis: Since the first clinical gene therapy trial was performed at the NIH in 1990, 50 additional institutions have cleared 148 gene therapy and gene marking protocols through the NIH Recombinant DNA Advisory Committee (RAC).

These Phase I trials were designed to test the feasibility and safety of administering gene-containing vectors to humans. Accordingly, the clinical efficacy of gene therapy in humans has yet to be clearly established and it remains as a complex challenge to bring this powerful technology with its great potential into clinical practice.

The targeted diseases to date are primarily cancer, cystic fibrosis and AIDS but additional diseases are also being investigated.

The hurdles that these investigations must clear are both formidable and appropriate:

1. The gene to be inserted in the patient's cells must first be identified from the vast array of other genes present within the human genome. It must then be cloned and induced to reproduce itself multiple times to provide a large number of copies. These gene copies are then spliced into the middle of another stretch of different genes that control the function of the desired gene. This hybrid is the desired vector. The steps to this point are complex and include the basic research and goal-directed development of a vector useful in one specific disease.
2. Subsequently, the vectors are induced to reproduce and generate billions of copies for use in the patients. This step must be performed under Good Manufacturing Practice (GMP) conditions, a demanding and expensive procedure required to protect the patient from exposure to dangerous extraneous agents that could otherwise appear if the care imposed by such stringent operating conditions did not exist. The GMP conditions entail use of approved equipment and reagents, extreme cleanliness, sterile conditions, exquisite record keeping to document the aforementioned demands, and specially designed facilities that will permit this production to proceed under these constraints. The cost of establishing such an operation can exceed \$1 million.

The daunting requirements of making large quantities of clinical grade vectors have been addressed by both academic institutions and commercial organizations that have developed Good Manufacturing Practice procedures and facilities to generate clinical grade vectors for their own use.

However, the vectors produced by these institutions are not always available to, nor of interest to, other clinical investigators. And often, the organizations that have these GMP facilities may not be able or willing to provide vectors for the unique protocols of other investigators. This certainly is due in part to the large amounts of money that they have spent to develop these technologies. In the case of commercial organizations, the pay out for them will be to develop vectors that will be useful in treating large numbers of patients that have common diseases. As a result, clinical investigators who have developed innovative protocols to treat uncommon or rare diseases are likely to experience difficulty in obtaining adequate quantities of clinical grade vectors for these investigational protocols.

Many rare diseases are expressions of an error in a single gene and as such may serve as a more clear cut target for gene therapy than the complex and more common diseases. So while these rare diseases may not provide the financial incentive seen as necessary by

a commercial organization, these diseases will more likely be studied by academic investigators for compelling scientific reasons and eventually provide clear and more rapid determinations of the success or failure of that gene therapy protocol.

The procedures listed in (1) above are the basic research and goal-directed development required to identify a usable vector for treatment of a specific disease and, while costly, are not daunting and routinely performed at the research institution. However, generation of usable quantities of vectors as described in (2) require GMP procedures and facilities that are very expensive and not routinely available to academic institutions or small businesses.

The NCRR recognized the unavailability of vectors as a problem. Academic clinical investigators needed a responsive resource from which large batches of clinical grade gene vectors could be obtained without requiring that their own institution build a GMP facility to produce the needed quantities of the desired vector.

Accordingly, the NCRR, together with the National Cancer Institute, National Heart, Lung, and Blood Institute, and National Institute of Diabetes and Digestive and Kidney Diseases, and with co-funding from the Office of AIDS Research established the National Gene Vector Laboratories (NGVLs) at the Indiana University, the University of Pennsylvania and the University of Michigan to produce large-scale quantities of vectors for clinical use by other qualified investigators in approved gene therapy protocols.

The NGVLs have established the GMP facilities and procedures and now provide these resources to clinical investigators who need large quantities of clinical-grade vectors. The cost of establishing a GMP production facility and its standard operating procedures has thus been borne by the NGVLs, enabling academic institutions and small businesses to have their vectors produced under GMP conditions without incurring the costs of establishing their own GMP operation which would drive up the cost of the vector.

Gene therapy has extraordinary potential in the long-term. The realization of this long-term goal requires proper development of its scientific bases and validation of its utility to patients by means of carefully designed, controlled and evaluated clinical trials. It is the intent of the NGVL program to facilitate the attainment of this goal.

SHARED INSTRUMENTATION

Mr. Porter: What is the average shelf life of the biomedical research equipment that is purchased through your shared instrumentation program? Has that changed substantially in the last decade?

Dr. Vaitukaitis: A recent survey of users of equipment provided by the Shared Instrumentation Grant (SIG) program showed that 83 percent of the one-year old instruments were judged to be state-of-the-art, which was almost double (49 percent) the

percentage for seven year old instruments. The rapid pace of technological development is illustrated by the fact that 40 percent of the SIG instruments had undergone a significant upgrade (to enhance instrument capability and performance), and 69 percent of these upgrades occurred within the first four years of the award. Four percent reported an upgrade the same year as the award.

Mr. Porter: Are the number of applications for the shared instrumentation grant program increasing because of the cost of equipment and the belt-tightening that is occurring in academic health centers?

Dr. Vaitukaitis: Academic health centers have been particularly impacted by health care reform and are not likely to be in a position to underwrite the costs of expensive instrumentation in the near future. Also, increasing financial constraints have made sharing essential and highlight the need for broad-based institutional initiatives such as the SIG program which allows expensive instrumentation to be shared by a large number of independent NIH-supported investigators in a cost-effective manner.

The application pressure for the SIG program is driven by several considerations including the rate of obsolescence of existing equipment and the emergence of new technologies. The single most influential factor is that the amount of data being sought is increasing drastically (that is, because of the increase in the number of genome projects, the number of x-ray crystallography studies, etc). New instruments and modalities are available to determine how biomolecules work, and help researchers understand the relationships between structure and function. This need has grown more urgent because these modern capabilities are needed by an ever increasing number of biochemists, virologists, glycobiologists, microbiologists, radiologists, immunologists, gene therapists and molecular biologists. New state-of-the-art instruments with improved capabilities are crucial to allow investigators to solve problems that are difficult or not approachable with previous conventional technologies and to keep them at the forefront of the field.

PRIMATE RESEARCH CENTERS

Mr. Porter: How much funding do the regional primate centers receive from other Federal agencies? From their home institution?

Dr. Vaitukaitis: According to the most recent survey (July, 1995), core and collaborative scientists at the seven Regional Primate Research Centers received research awards in FY 1995 totaling \$14.26 million from other Federal agencies (e.g. NSF, FDA, NASA). These funds represented approximately 6.0 percent of a grand total (funds received from all sources) of \$238.59 million. The vast majority of this grand total, or 73.1 percent, was received from the NIH categorical institutes and centers. Funds received from the seven Centers' host academic institutions totaled \$13.56 million (i.e. 5.7 percent of the grand total). The remainder of funds was received from private foundations (6.0 percent); industry (7.9 percent) and other sources (1.3 percent).

EXTRAMURAL FACILITIES CONSTRUCTION

Mr. Porter: The authorizing law mandates a 25 percent set-aside of the extramural facilities grant program for historically black institutions and other institutions of emerging excellence. Why do you consider applications from these institutions in the same pool as general applications rather than setting aside 25 percent of the appropriation and having them compete against each other for that pot of funding?

Dr. Vaitukaitis: The NIH Revitalization Act of 1993, which authorizes the extramural facilities construction program, provides in Sec. 481A, subsection (c), paragraph (1) the review requirements for all construction applications received, including those received from Institutions of Emerging Excellence. Paragraph (3) of subsection (c) of the law states that "Of the amounts appropriated...the Director of the Center shall make available 25 percent for grants...to applicants that, in addition to meeting the requirements established in paragraph (1), have demonstrated emerging excellence in biomedical and behavioral research...." Clearly the intent of the authorizing language is that all construction awards to be made under the program meet the same requirements.

Institutions of Emerging Excellence can compete successfully with other, more established research institutions. This was proven the first year of the construction program when applications from two of these institutions scored well and were funded.

BIOMEDICAL RESEARCH SUPPORT

Mr. Porter: Provide a breakout of the Biomedical Research Support program line for FY95-97.

Dr. Vaitukaitis: As a result of a recent NCRR reorganization, the Biomedical Research Support program no longer exists. The Biomedical Research Support entry on the NIH mechanism table includes the following components:

	FY 1995	FY 1996	FY 1997
Minority High School Student Research Apprentice	\$4,782,000	\$0	\$0
Minority K-12 Initiative	\$2,557,000	\$4,414,000	\$3,604,000
Shared Instrumentation Grant	\$9,868,000	\$20,500,000	\$20,500,000
Total	\$17,207,000	\$24,914,000	\$24,104,000

PROGRAM FUNDING

Mr. Porter: Provide the FY95-97 funding for: IDeA; primate centers; biological models and materials; and animal facilities improvements.

Dr. Vaitukaitis: Funding for these activities is as follows:

	FY 1995	FY 1996	FY 1997
Institutional Development Award	\$930,000	\$2,100,000	\$2,100,000
Primate Centers	\$43,290,000	\$44,974,000	\$44,374,000
Biological Models & Materials Research	\$10,078,000	\$11,880,000	\$12,690,000
Animal Facilities Improvement	\$3,717,000	\$3,817,000	\$3,817,000

CLINICAL RESEARCH

Mr. Porter: We understand that your clinical research centers also receive some support from the Veterans Administration and NASA. How much do these other agencies contribute and for what purposes?

Dr. Vaitukaitis: In FY 1995, our General Clinical Research Centers (GCRC) Program received \$350,000 from NASA. These funds were awarded to two GCRCs, at the University of Texas Southwestern Medical School in Dallas, and the University of Texas Medical Branch in Galveston, for NASA-based research projects. NASA funds helped offset the costs of those studies. The NASA-supported studies primarily focused on physiological changes, such as muscle atrophy and bone demineralization, occurring in volunteers during prolonged bed rest, as a model for the microgravity experienced in space. Both in space, and upon prolonged bed rest, calcium leaches out of bones, and this can lead to the formation of calcium-containing kidney stones. In one NASA-supported GCRC study, it was shown that administration of the drug alendronate protected against bone demineralization and kidney stone formation. NASA has contributed no funds in FY 1996.

One of the 75 GCRCs is located entirely within a Veterans Administration (VA) hospital, the Audie Murphy Memorial Hospital in San Antonio, Texas. Other GCRCs, while located primarily at university medical centers, conduct some studies in "satellite" VA Hospital facilities. The GCRC program reimburses the cost of the clinical research days on a per diem (per bed day use) basis and also reimburses the VA for outpatient and

administrative space charges. The GCRC program also supports the paramedical and administrative staff needed to operate the GCRC. Research areas studied at these GCRC-VA locations include cancer, diabetes, AIDS, and schizophrenia, usually supported by NIH categorical institutes.

INSTITUTIONAL DEVELOPMENT AWARDS

Mr. Wicker: Dr. Vaitukaitis, this Committee for a number of years has included report language endorsing NCRR activities to expand the research capacity in States which have not traditionally participated as heavily as others in NIH programs. This program is called the Institutional Development Award program or IDeA. Can you update the Committee on your plans for this program in 1996 and under the President's 1997 request.

Dr. Vaitukaitis: The Institutional Development Award activity received an appropriation of \$2.1 million in FY 1996. A Program Announcement soliciting research grant applications from eligible states was published in December, 1995 with a February 1 receipt date. The matching awards are to be for up to three years at a level not to exceed \$200,000 per year direct costs from the NIH. Twelve states submitted applications. These were reviewed for scientific and technical merit in April, and are to be considered by the National Advisory Research Resources Council in September for the second level of review. The requested level of funding in the President's FY 1997 budget request is \$2.1 million; this will allow continued funding of the 1996 awards.

Mr. Wicker: It is our understanding that all IDeA projects are chosen competitively. Is that correct?

Dr. Vaitukaitis: Yes. All Institutional Development Awards applications are reviewed for scientific and technical merit by an Initial Review Group of peers, and undergo a second level of review by the National Advisory Research Resources Council.

Mr. Wicker: Several years ago the Center completed a report which indicated that an expansion of the IDeA capacity building program to a level of \$20 million per year would be appropriate if the money could be found to add to NIH's budget. Do you still believe this level of funding could be effectively spent.

Dr. Vaitukaitis: The plan submitted several years ago for implementing the IDeA program at NIH included a phase of institutional planning grants, followed by a phase of competition for funds set aside within all the Institutes and Centers in mechanisms that are in general use at the NIH. Currently, the NCRR is making developmental awards to several institutions each year, but no funds have been specifically identified for these institutions within the existing grant mechanisms. If funds could be found to add to the NIH budget for this purpose, I believe that we could effectively use from \$15,000,000 to \$20,000,000.

Mr. Wicker: We are aware that a number of researchers have indicated that the eligibility criteria for States to participate in the IDeA program unintentionally excludes certain States by using a very narrow definition of a State's success rates in winning NIH grants. Is NCRR willing to reconsider this definition?

Dr. Vaitukaitis: The authorization language from the NIH Revitalization Act of 1993 (Section 202) indicates that the program is intended for states in which the aggregate success rate for grant applications for NIH funding from research institutions in the state have historically constituted a low success rate in obtaining such funds related to aggregate rates in other states. The NCRR defined the 15 eligible states as those with success rates for obtaining NIH funds of less than 20 percent for the period 1982-1994. This criterion conforms to the intent of the authorizing legislation. The NCRR would certainly be willing to consider other criteria that meet this intent.

Mr. Wicker: Would it make sense for NIH to use the same system of State eligibility for IDeA which NSF uses for the EPSCoR?

Dr. Vaitukaitis: The distribution and competitiveness of states for NIH and NSF grant funds are not the same, and a separate determination of eligibility for IDeA awards and EPSCoR awards reflects those differences.

EXTRAMURAL CONSTRUCTION

Mr. Stokes: To meet the clear legislative intent of this 25 percent designation, does the NCRR have a specific plan that would help facilitate this directive -- perhaps something that could be initiated to level the playing field?

Dr. Vaitukaitis: The NCRR contacted each Center of Emerging Excellence regarding the availability of the Request for Applications. In addition, assistance was offered to these institutions in the preparation of their applications. These centers are well represented on the panel of initial reviewers, as well.

Section 481A of the NIH Revitalization Act requires that all applications, including those from Centers of Emerging Excellence, be reviewed by the Board established under the section, and that applicants meet "reasonable qualifications established by the Director with respect to--(I) the relative scientific and technical merit of the applications." The Section also stipulates that only applications approved by the Board may be considered for funding by the Director.

To provide more positive feedback to applicants regarding the review of their proposals, the NCRR has decided that all FY 1996 applications will be accorded a full Board initial merit review. This represents a change from the prior year in which applications were judged competitive or non-competitive, with competitive applications receiving a full Board discussion and review.

SCIENCE EDUCATION

Mr. Stokes: What progress are you able to report with regard to the minority students and teachers kindergarten through grade twelve initiative?

Dr. Vaitukaitis: The phase-in of the new "NCRR Minority Initiative: K-12 Teachers and High School Students," begun in FY 1994 to replace the Minority High School Student Research Apprentice Program (MHSSRAP), was completed this year (FY 1996). A new, ongoing Program Announcement -- with two application submission dates for this and future years -- was published on April 19, 1996. From 73 grant awards in FY 1994, the initiative has grown to 102 awards in FY 1996.

Mr. Stokes: What is the future of the science education partnership award program?

Dr. Vaitukaitis: The Science Education Partnership Award (SEPA) program has been supported and managed by NCRR since 1991. In FY 1995, a total of \$2,892,366 was awarded to 14 grantees to facilitate the completion, evaluation and dissemination of innovative and interactive educational models designed to stimulate the interest of students in biomedical and behavioral science and/or the health-related science literacy of the general public. The NCRR expects to make 15 SEPA awards in FY 1996 totaling about \$3.3 million. The Office of Science Education, Office of the Director (OSE/OD),

NIH, has been a major contributor to this program in FY 1994, 1995 and 1996, providing \$1,000,000 in each of these years.

The NCRR plans to continue the SEPA Program for the foreseeable future. A Program Announcement has been developed, inviting applicants to submit proposals to generate new models for biomedical science education or distribute existing ones that are effective. A total of \$1.5 million has been requested for NCRR's SEPA program in FY 1997. Even though the OSE/OD has indicated that other urgent priorities will prevent that office from contributing funds for this SEPA program in FY 1997, NCRR's commitment will assure that the most meritorious health science education proposals will be supported in FY 1997.

MINORITY CLINICAL INVESTIGATORS

Mr. Stokes: How is the center addressing the need to develop and train more minority clinical research investigators?

Dr. Vaitukaitis: The Center is addressing this need through the General Clinical Research Centers (GCRC) and Research Centers in Minority Institutions (RCMI) programs. Within the GCRC program this is being done through a modification of the Clinical Associate Physician (CAP) program, which provides up to three years of support to physicians or dentists to promote their development toward independent clinical investigators. The Minority Clinical Associate Physician (MCAP) program, which made its first awards in 1991, also provides up to three years of support and is designed to attract underrepresented minority scientists to careers in clinical research. A senior clinical scientist serves as the mentor. To date, 25 awards have been made. Additionally within the GCRC program, the Clinical Research Scholar (CRS) program was initiated in FY 1996. This program provides support for one year of course work and mentored clinical research. Underrepresented minorities can compete for funding from CRS as well as CAP programs.

In addition to the career development programs described, all minority clinical research investigators are encouraged to participate in regular ward rounds, seminars, workshops, lectures and courses sponsored by and conducted under the auspices of the GCRCs. Irrespective of their funding status, they are welcome to conduct pilot patient-oriented studies on the GCRCs once the studies have been approved by the local GCRC Advisory Committee. If they have peer reviewed funding, they can then apply to the GCRC Advisory Committee for utilization of the GCRC infrastructure (inpatient and outpatient facilities, nursing and dietary care, bio-statistics and computer systems analysis of data) for their projects. The work can be conducted independently or under the supervision of a well trained, experienced mentor in clinical investigation.

Through the RCMI Clinical Research Infrastructure Initiative, which was initiated October 1, 1995, faculty at minority institutions that award doctoral degrees compete for

support to conduct pilot clinical research. This will enable these scientists to obtain preliminary data that can be used to compete for independent research support.

EXTRAMURAL CONSTRUCTION

Mr. Stokes: So after a thorough study and assessment of the Nation's research facilities in research institutions across the country, you determined that their facilities now meet some well defined criteria that led you to eliminate the program? Explain in detail and provide a listing of the studies and reports that were researched and used to help make this determination?

Dr. Vaitukaitis: The Extramural Construction program of the NCRR was proposed for elimination in FY 1997 as a result of competing priorities for limited funds. Funding has been requested to build a replacement facility for the NIH Clinical Research Center, and to maintain the NIH commitment to investigator-initiated research project grants. There have been no studies that indicate that the need for research facility construction has disappeared.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Stokes: To what extent has the center been able to generate co-funding of the programs and research at the research centers in minority institutions by the other NIH Institutes and centers?

Dr. Vaitukaitis: The NCRR's Research Centers in Minority Institutions (RCMI) Program has collaborated with many other NIH Institutes and Centers, including the National Institute of Allergy and Infectious Diseases (NIAID), the National Center for Human Genome Research (NCHGR), the National Institute of Environmental Health Sciences (NIEHS), the National Heart, Lung and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), the National Institute for Dental Research (NIDR) and the Office of Research on Minority Health (ORMH).

The nature of these collaborations has been varied and far-reaching. Included among these activities are the joint participation of NCRR and other NIH components in symposia, meetings and planning conferences, cofunding of RCMI program activities, and sponsorship of RCMI faculty participation in selected workshops. Also, NIH institutes and centers have facilitated the development of collaborative and consultative research relationships, and have developed program announcements and other requests for applications that focus on diseases that disproportionately impact minority populations. Scientists at RCMI institutions have been particularly encouraged to compete for these resources.

In FY 1995, a total of \$5,406,821 was received via cofunding from ORMH (\$2.5 million), NIAID (\$2.72 million), and other NIH components (\$.18 million) for RCMi program activities. This represented an increase in NCRR-managed resources for the RCMi grantee community of 21.2 percent above the congressional appropriation. The development of research infrastructure for the conduct of clinical trials and the participation of RCMi grantees in these nationally coordinated clinical investigations are among other major institutes' contributions. For example, four RCMi grantees are currently involved as members of the national network of AIDS Clinical Trial Units (ACTUs). In addition, the four HBCU medical schools are participants in the national study on the effect of different treatment modalities on the course of end stage renal disease in African-Americans, supported by NIDDK.

Involvement in the NIH agenda for research related to AIDS by RCMi grantees has increased over 24-fold from FY 1988 (\$0.6 million) to FY 1995 (\$14.86 million). The FY 1995 support was obtained competitively from the RCMi appropriation (\$3.51 million), NIAID cofunding (\$2.72 million), and other NIH sources (\$8.63 million).

Since a major goal of the RCMi program is to enhance the competitiveness of biomedical and behavioral scientists at RCMi institutions, NCRR will continue its efforts to expand the participation of the RCMi community in the programs and activities of the other NIH Institutes and Centers in FY 1996, 1997 and beyond.

Mr. Stokes: Over the years, what impact has the research centers in minority institutions program had at the institutions supported by the program?

Dr. Vaitukaitis: The RCMi program support has facilitated research collaborations, has been invaluable in recruiting additional research faculty, facilitated the development of new Ph.D. programs, and increased the ability of faculty to obtain extramural research support. With respect to the latter, the NIH research support now available to the RCMi grantee community has increased from \$28.3 million in FY 1984 to \$94.5 million in FY 1995, approximately a 234 percent increase since the initiation of the RCMi Program. Some examples of collaborative studies now underway are: (a) assessing the difference in the HIV viral populations in Ugandans in order to determine the potential efficacy of emerging vaccines; (b) evaluating the role of three different drugs and two different blood pressures on the progression to end-stage renal disease in African Americans; (c) participation in the landmark clinical trial which demonstrated the efficacy of AZT in forestalling the transmission of HIV from mother to child; and (d) the development of an African American Reference Family Panel of genetic data to help scientists identify gene-based differences among population subgroups in their sensitivity to drugs, a number of diseases such as vitiligo, cancer, and diabetes and immune response.

One mechanism used to increase the RCMi-eligible institutions' competitiveness is providing direct support to hire new research faculty. These faculty are provided start-up costs to support their research and funds are provided to renovate appropriate space. A number of the faculty recruited to date have competed for investigator-initiated research

grants and training grants. The expanded faculty research competence has assisted in developing new Ph.D. programs in molecular biology, neurophysiology and pharmacology. The doctoral program in neurophysiology in 1993 graduated two African American Ph.D.s, both of whom were also awarded M.D.s. They were the only two African Americans awarded Ph.D.s in 1993.

CLINICAL RESEARCH AT MINORITY INSTITUTIONS

Mr. Stokes: To what extent has the center implemented activities to address the need for developing the infrastructure for clinical research at minority institutions?

Dr. Vaitukaitis: After two years of planning, with substantial input from the eight RCMI-eligible institutions with affiliated medical schools, five institutions were successful in competing for funds to assist them in developing their clinical research infrastructure.

These five year awards, at an average direct cost of \$600,000, were made September 30, 1995, through the RCMI Clinical Research Infrastructure Initiative (RCRII). They provide critical staff resources (nursing staff, biostatisticians, epidemiologists, computer specialists, technical support and data entry clerks), support for pilot clinical research projects, external advisors/evaluators and renovations. Plans are now underway to develop a MCAP-like program which will facilitate the development of the clinical research skills of faculty now in residence at these institutions. One of the other institutions is now competing for support through the RCRII. Another is competing for a GCRC award.

MINORITY RESEARCH INVESTIGATORS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under its purview?

Dr. Vaitukaitis: In FY 1995, after two years of planning, NCRR, along with support from ORMH, provided support to 5 RCMI-eligible institutions that have affiliated medical schools. These five-year awards, through the RCMI Clinical Research Infrastructure Initiative, will enable the grantee institutions to expand their involvement in clinical research by hiring additional clinical faculty, supporting pilot projects and having available personnel (biostatisticians, epidemiologists, nurses, technicians and administrative assistants). These pilot clinical research projects are particularly relevant to the health of minorities and women. Some examples include hypertension, infant mortality, cancer prevention and control, lupus, AIDS, and epilepsy.

Long-range, it is anticipated that this initiative will increase the number of minority investigators with clinical research awards, thereby helping to develop an expanded capacity to obtain extramural support for a clinical research center.

Through NCRR's collaboration with the NIDR, we are providing support for faculty development to two RCMI-eligible institutions. This support is facilitating the development of an expanded faculty research competence in the NIDR funded Regional Research Centers for Minority Oral Health. One of the objectives is to "enhance the research capabilities and participation of members of racial and ethnic minorities in health research."

In FY 1995, the NCRR cofunded 1 of 9 grant applications submitted in response to the NIAID-sponsored RFA entitled "Enhancement Awards for Underrepresented Minority Researchers in HIV/AIDS." The goal is to enable these investigators to establish clinical or basic AIDS research programs. The grants foster collaboration between more established investigators and the minority investigator to enhance refinement and maximize the chances of success. The NCRR-supported investigator's research is a pharmacokinetic study of intracellular AZT in children.

Mr. Stokes: What efforts has your Institute undertaken to educate minorities on opportunities that are available in biomedical research?

Dr. Vaitukaitis: In FY 1995, in conjunction with the Office of Research on Minority Health (ORMH), the NCRR launched a new program, the Research Infrastructure in Minority Institutions (RIMI) program. The program's objectives are to facilitate the participation of the nondoctoral degree-granting minority institutions in biomedical/behavioral research by improving their research infrastructure. Each applicant must develop formal collaborative agreements with research intensive doctoral degree-granting institutions. This is intended to facilitate research and mentoring interactions between the faculties in grantee and collaborating institutions. Increased participation of students from the grantee institution in the doctoral programs is an anticipated benefit of these collaborations.

After a two-day grantsmanship workshop, sponsored by ORMH and NCRR, which involved 57 participants from 32 eligible institutions, 27 applicants are now competing for funding. It is now anticipated that 5-7 five-year awards will be made. The ORMH has committed \$4,000,000 per year for five years to support this exploratory initiative.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at the center? How much is included in the FY97 budget for the center's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Vaitukaitis: In October 1995, NCRR launched its Home Page on Internet via the World Wide Web. The purpose of the NCRR Home Page is to help the biomedical research community more easily access NCRR's nationwide networks of shared research

resource centers, facilities, technologies, biomaterials, and animal models. The NCRR Home Page proved to be a valuable communication tool for grantees and others by providing needed information about research resources during the partial government shutdown last winter.

NCRR publishes the NCRR Reporter, an award-winning bimonthly magazine that keeps abreast of state-of-the-art clinical, biomedical technology, and primate research centers, as well as other research resources supported by NCRR. Since 1977, the NCRR Reporter has generated wider use of these resources, greater communication among users, and more collaborative and imaginative use of NCRR-supported resources and technologies. Targeted audiences include biomedical researchers, government and university administrators, representatives of the private sector, the media, science educators, and educated laypersons.

NCRR also publishes three directories: Clinical Research Resources, Biomedical Technology Resources, and Mammalian Models for Biomedical Research. Each directory lists dozens of NCRR-supported resource centers available to biomedical investigators throughout the U.S. The directories describe current research programs at the centers and resources available to qualified investigators.

In FY 1994, NCRR produced a video, NCRR: A Catalyst for Discovery, to help make biomedical investigators aware of valuable resources and technologies that could aid their research, and to encourage collaboration. This award-winning video features NCRR-supported activities--from clinical studies to high-tech instrumentation, minority programs, science education, and animal models for human disease.

NCRR also supports the Science Education Partnership Award program, whose purpose is to encourage scientists to work together with educators and other organizations to improve student (K-12) and public understanding of the health sciences. The model programs span the range of science education, including a national video education program, a traveling AIDS museum exhibit, biotechnology research experiences for students and teachers, and health promoting outreach programs for inner city and rural communities.

The FY 1997 President's Budget request includes approximately \$700,000 for NCRR's public information efforts, about the same level as in FY 1995 and FY 1996, and a reduction of about \$50,000 from the FY 1994 level. The request includes \$1,500,000 for the Science Education Partnership Awards. The FY 1994, 1995, and 1996 NCRR levels for this programs were \$760,000, \$2,000,000, and \$2,500,000, respectively.

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account. Is this the case in your center? If yes, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Vaitukaitis: Most of our outreach and public education programs are funded through the research management and support account. We have not been able to maintain these programs at previous levels, but have continued to support these activities. The Science Education Partnership Award program is funded through grants.

OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: What collaborative efforts are underway between the center and the Office of Research on Minority Health? Are there specific projects in your center that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Vaitukaitis: The Office of Research on Minority Health (ORMH) and the NCRR have been collaborating on programs of mutual interest for several years. Areas have included the Environmental Health Sciences and Toxicology initiative and the Clinical Research Infrastructure Initiative, both within the Research Centers in Minority Institutions (RCMI) program, the Minority Clinician Associate Physician program of the General Clinical Research Centers (GCRC) program, the NCRR Minority Initiative: K-12 Teachers and High School Students, and the Research Infrastructure in Minority Institutions (RIMI) program.

In FY 1995, 14 planning grants were awarded for the new RIMI initiative, a collaborative program between NCRR and ORMH to expand biomedical research capability at minority institutions granting masters and baccalaureate degrees. These Phase I planning grants, totaling \$914,179, were fully funded by ORMH.

The grantee institutions, project periods, and amounts of funding are listed below:

Grantee Institution	Project Period	Dollars Awarded
Alabama A&M University	9/95 - 9/96	\$62,933
Benedict College	9/95 - 9/96	62,100
California State Univ, Dominguez Hills	9/95 - 9/96	68,857
California State Univ, Los Angeles	9/95 - 9/96	65,267
Fisk University	9/95 - 9/96	65,459
Hampton University	9/95 - 9/96	75,650
Inter American University of Puerto Rico	9/95 - 9/96	68,138
Langston University	9/95 - 9/96	58,403
Morgan State University	9/95 - 9/96	70,333
St. Mary's University	9/95 - 9/96	49,814
Spelman College	9/95 - 9/96	75,308

Texas A&M University, Kingsville	9/95 - 9/96	63,145
University of the District of Columbia	9/95 - 9/96	66,455
Winston-Salem State Univ	9/95 - 9/96	62,317

TOTAL DOLLARS, FY 1995 AWARDS (RIMI program) \$914,179

In FY 1996, ORMH and NCRR are collaborating to support about five to seven Phase II RIMI awards for implementation of plans for infrastructure development. A total of 27 applications have been received from eligible minority institutions, each requesting up to \$600,000 direct costs per year for up to five years. These applications are currently in the review process. The ORMH plans to contribute \$4,000,000 for the first year of this initiative, and NCRR intends to provide additional support, if necessary, to support highly meritorious proposals.

The NCRR and ORMH expect to collaborate throughout the five-year funding period for these RIMI Phase II implementation awards.

There are eleven currently active K-12 grants funded totally by the Office of Research on Minority Health in order to increase the number of students and teachers able to be supported by, and benefit from, the K-12 Initiative. They were funded totally by the Office in order that the K-12 Initiative commitment base for future years not be increased beyond the level of anticipated NCRR fund availability, and were all awarded in FY 1994.

The grantee institutions, project periods, and amounts of funding are listed below:

Grantee Institution	Project Period	Dollars Awarded
Baylor College of Medicine	9/94 - 9/97	\$110,522
Brandeis University	9/94 - 9/97	89,910
Charles R. Drew University	9/94 - 9/97	172,841
Kennedy Krieger Research Institute, Baltimore	9/94 - 9/97	102,913
Medical College of Wisconsin, Milwaukee	9/94 - 9/97	138,089
Michigan Cancer Foundation, Detroit	9/94 - 9/97	122,846
Rutgers University	9/94 - 9/97	151,015
UMDNJ-New Jersey Medical School, Newark	9/94 - 9/97	182,545

University of Michigan, Ann Arbor	9/94 - 9/97	139,451
University of Mississippi	9/94 - 9/97	149,179
University of Texas, El Paso	9/94 - 9/97	128,166

TOTAL DOLLARS, FY 1994 AWARDS (K-12 Initiative)\$1,487,477

In FY 1995, ORMH also provided NCRR funds to support five Minority Clinical Associate Physician (MCAP) awards. These awards are made as competitive supplements to General Clinical Research Center grants and can provide for a maximum of three years of support.

Grantee Institution	Dollars Awarded
Brigham & Women's Hospital	\$30,417
Stanford University	16,598
Vanderbilt University	34,944
University of California, Los Angeles	32,783
University of Alabama	36,582

TOTAL DOLLARS, FY 1995 AWARDS (MCAP program) \$151,324

The NCRR and ORMH expect to collaborate throughout the award period.

Mr. Stokes: Are there specific projects that are co-funded by the center and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the center and the office.

Dr. Vaitukaitis: FY 1995 was the first year of the RCMI Clinical Research Infrastructure Initiative (RCRII). This initiative was developed in response to FY 1993 appropriation language requesting that efforts be made to improve the clinical research infrastructure at RCMI institutions, and is the culmination of a two-year planning process, utilizing the GCRC community's extensive experience and input from RCMI grantees with affiliated medical schools.

In FY 1995, major support for the first year of this five-year program was provided by ORMH (\$2,582,768) in addition to \$997,280 provided by NCRR and \$156,501 in NIAID cofunding, for a total of \$3,736,629. By pooling their resources to achieve mutual goals, these NIH components were able to fund all five of the RCRII applications that had competed successfully through the review process.

The grantee institutions, budget periods, and amounts of funding are listed below:

Grantee Institution	Budget Period	Dollars Awarded (Percent)		
Charles R. Drew University of Medicine & Science	9/95 - 9/96	ORMH	\$500,000	(65)
		NCRR	266,835	(35)
Morehouse School of Medicine	9/95 - 9/96	ORMH	500,000	(65)
		NCRR	265,978	(35)
Universidad Central del Caribe	9/95 - 9/96	ORMH	500,000	(62)
		NCRR	203,591	(25)
		NIAID	100,631	(13)
University of Hawaii at Manoa	9/95 - 9/96	ORMH	500,000	(73)
		NCRR	131,917	(19)
		NIAID	55,950	(8)
University of Puerto Rico, Medical Sciences Campus	9/95 - 9/96	ORMH	582,768	(82)
		NCRR	128,959	(18)
TOTALS	ORMH	\$2,582,768	(69)	
	NCRR	997,280	(27)	
	NIAID	156,581	(4)	
TOTAL		\$3,736,629		

The NCRR, ORMH and NIAID will continue to collaborate on this critically important initiative throughout the five-year project period. The NCRR is planning on a much larger financial contribution in FY 1996; current estimates are \$3,500,000 for support of the second year of the program.

There is one active K-12 grant funded by the Center and the Office of Research on Minority Health. This grant was co-funded by ORMH in order to increase the number of students and teachers able to be supported by, and benefit from, the K-12 Initiative.

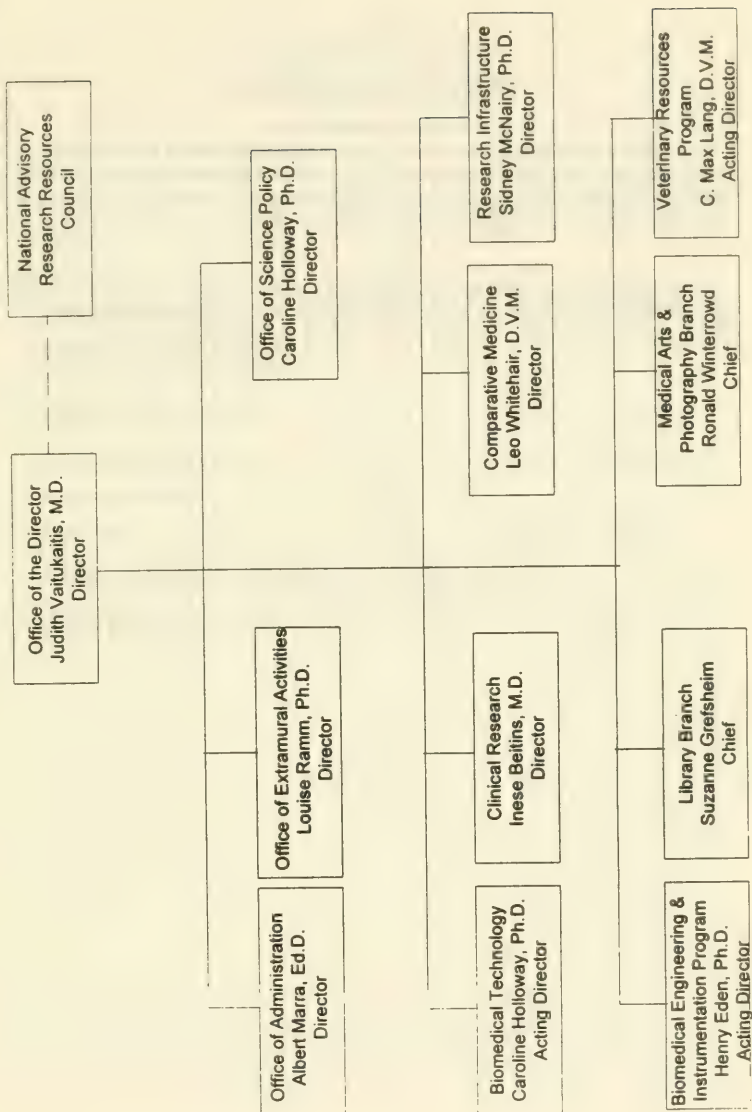
The grantee institution, budget period, and amounts of funding are listed below:

Grantee Institution	Budget Period	Dollars Awarded (Percent)		
State University of New York, Buffalo	9/94 - 9/97	ORMH	\$13,523	(15)
		NCRR	74,189	(85)

JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

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NATIONAL INSTITUTES OF HEALTH
National Center For Research Resources
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

For carrying out section 301 and title IV of the Public Health Service Act with respect to research resources and general research support grants; \$309,344,000: Provided, That none of these funds shall be used to pay recipients of the general research support grants program any amount for indirect expenses in connection with such grants.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Amounts Available for Obligation 1/

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Appropriation	\$294,877,000	\$390,339,000	\$309,344,000
Enacted reduction, P.L. 103-333.....	(140,000)		
Enacted rescission, P.L. 104-19.....	(10,044,000)		
Subtotal, adjusted appropriation.....	284,693,000	390,339,000	309,344,000
Real Transfer from other NIH Institutes through the NIH Director's one percent transfer authority.....	2,648,000		
Comparable transfer to the Office of AIDS Research, NIH for HIV Activities.....		(68,370,000)	
Subtotal, adjusted budget authority.....	287,341,000	321,969,000	309,344,000
Unobligated balance, lapsing.....	(48,000)		
Total, obligations.....	287,293,000	321,969,000	309,344,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1995 - \$7,293,000; and FY 1996 - \$9,000,000; and FY 1997 - \$9,000,000.

Also excludes funding for HIV activities: FY 1995 - \$64,630,000; FY 1997 - \$88,255,000, included in
the Office of AIDS Research, NIH.

National Center for Research Resources

Authorizing Legislation - Sections 301, 479, and 487 of the Public Health Service Act. 1997
Authorization: Indefinite.

Budget Authority:

FY 1995		FY 1996		FY 1997		Increase or Decrease	
Actual		Current Estimate		Estimate			
FTE	BA	FTE	BA	FTE	BA	FTE	BA
98	\$287,341,000	96	\$321,969,000	96	\$309,344,000	--	-\$12,625,000

This document provides justification for the FY 1997 Non-AIDS activities of the National Center for Research Resources. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Purpose and Method of Operation

The National Center for Research Resources funds the development, support and provision of shared research resources and technologies, as well as the enhancement of research capacity, through its extramural programs. Most of these crosscut the entire range of the Center's mission, utilizing a variety of funding mechanisms for institutional and investigator support. Resource centers constitute the largest proportion of the Center's budget, and provide support to nationwide networks of centers for conducting cost-effective clinical research, for accessing state-of-the-art biomedical research technologies, and for the purpose of conducting research in nonhuman primates and other animal or nonanimal models. The centers mechanism is also utilized to help enhance the research capacity of minority institutions throughout the U.S. Research project grants and resource-related research grants support innovative development of technologies, including animals and other models, as well as those related to biotechnology. Through other support mechanisms, NCRR provides state-of-the-art instruments to be shared by an average of 15 NIH-supported researchers, as well as an array of biological materials for use by investigators. NCRR also funds improvement of animal facilities, career development, and programs to encourage careers in science for underrepresented groups. NCRR provides training for research veterinarians and young clinical investigators, and addresses the underrepresentation of minorities in these areas. Research contracts provide a variety of resources to individual investigators.

Overall Budget Policy

The FY 1997 budget request for the National Center for Research Resources is \$309,344,000, a decrease of \$12,625,000 below the FY 1996 estimate of \$321,969,000. Within the request, a funding increase of \$4,000,000 will be provided for two NIH areas of special emphasis,

\$2,000,000 each for genetics in medicine, and advanced instrumentation and computers in medicine and research.

In the FY 1997 President's Budget Request, NCRR support for research project grants (RPGs) would increase by 21.2 percent over FY 1996. NIH plans to revise average cost increases identified in the Cost Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average and the average cost of competing RPGs would increase by no more than 2 percent over FY 1996. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 64 competing RPGs, an increase of 8 competing RPGs over FY 1996, and 228 total RPGs, an increase of 38 total RPGs over FY 1996.

The NCRR will support 187 research resource centers, with an increase of \$2,650,000 over the FY 1996 level. NCRR will maintain support to 76 general clinical research centers, 62 biomedical research technology centers, 7 regional primate research centers, 17 laboratory animal sciences centers, 6 biological models and materials research centers, and 19 research centers in minority institutions.

In the "Other Research" category, the shared instrumentation grants program will be maintained at the FY 1996 level of \$18,841,000, supporting 98 awards. In the minority initiative for K-12 teachers and high school students, 76 awards will be funded at a level of \$3,604,000. Approximately 12 science education partnership awards will be funded, at a level of \$1,500,000, and about 13 institutional development awards will be made for a total of \$2,100,000. Approximately 14 research career awards will be made, and there will be approximately 19 other research-related awards.

The FY 1997 request for research training is \$2,758,000, an increase of \$50,000 over the FY 1996 level, and will support approximately 72 institutional full-time equivalent training positions, and four individual fellowships. Funding will be provided for a modest stipend increase. The budget request for research and development contracts is \$2,991,000, a reduction of \$85,000 from FY 1996, supporting seven contracts. No funds are requested for the extramural construction program in FY 1997.

The FY 1997 budget request for Research Management and Support is \$13,015,000, the same level as in FY 1996. Approximately 96 FTEs will be supported, the same as in FY 1996.

Narrative Justification

The National Center for Research Resources (NCRR) creates, develops, and provides the infrastructure and tools of modern health-related science. Because these research resources and technologies are highly sophisticated and therefore costly, most are shared by many scientists.

NCRR's comprehensive range of shared human, technological, and animal resources include national networks of centers and programs that: (1) foster clinical research for a vast array of diseases in children and adults; (2) speed the development of sophisticated instrumentation and biotechnologies; (3) provide key models and biomaterials, including animal models, for studies of disease; and (4) expand the participation of underrepresented groups in biomedical research, including the development of the research capacity of minority institutions.

NCRR's shared resources are a national asset that offer many benefits to the biomedical research enterprise. These resources streamline the research process and lower its price tag by making the process more cost-effective and efficient. Each year, more than 10,000 researchers access NCRR resources, leveraging well over \$1.5 billion of Federal funding from the National Institutes of Health's (NIH) categorical Institutes and Centers. These shared resources enable multidisciplinary investigations ranging from basic research to multi-center clinical studies of new ways to prevent and treat diseases.

NCRR's clinical, biotechnology, and primate centers are scientific hubs. They promote public and private partnerships and collaborations that stretch scarce funding, encourage scientific sharing, and generate new approaches to health problems that exact huge human and economic losses. These centers have the capacity to undertake fast-track, high-risk research. These resources also help preserve the research scientist talent base through training and career development programs at clinical, primate, and other centers and resources.

SHARED RESOURCES

Clinical Resources

Most clinical research begins with the patient who presents with a constellation of medical problems that are poorly understood or for which no effective therapies may exist. Clinical research involves many different research activities to solve these complicated medical dilemmas. At one end of the spectrum is the direct interaction with the patient to characterize the disease process and define which tissues and processes are impacted. At the other is bench research to define the basis of disease and to develop novel diagnostic and therapeutic approaches to illness. Only after defining the mechanism of disease can effective treatments be designed. The clinical research focus then returns to the patient to test therapeutic response.

NCRR's nationwide network of about six dozen General Clinical Research Centers (GCRCs) provides the shared resources institutions need to conduct patient-centered research. Located primarily at academic medical centers throughout the United States, GCRCs provide state-of-the-art clinical research, laboratory, and computer facilities, as well as highly skilled staff. NIH-supported investigators can use these facilities to conduct novel clinical trials of new drug treatments, or multi-center investigations of the best way to address a specific human disease or disability. These GCRCs provide clinical research infrastructure where the results of laboratory research can be translated to new or improved therapies and prevention strategies.

Clinical research encompasses a wide array of research activities across many disciplines. Frequently, a controlled environment, staffed with specialized paramedical personnel, is required. Clinical research also requires a strong collateral basic research component for most studies. GCRCs provide infrastructure to academic institutions through the support of inpatient and outpatient research facilities and other resources vital for state-of-the-art patient-oriented research. The network of GCRCs also provides an effective forum for training and junior career development in clinical research.

Coronary artery disease is a leading cause of death for Americans. Recent findings indicate that low density lipoprotein (LDL)-lowering drugs plus antioxidants may help reduce the risk of heart attacks in people with coronary artery disease and high blood cholesterol levels. A study population, consisting of both men and women, was assigned different diets. After a year of treatment and testing in a General Clinical Research Center, investigators found that individuals on a combination of antioxidant and LDL cholesterol-lowering therapy had significantly lower total cholesterol and LDL cholesterol. This therapy had a beneficial effect on the ability of the circulation to bring more blood to the heart which reduces the risk of ischemia, or oxygen deprivation to the heart muscle.

Exercise electrocardiogram (ECG) screening can help physicians determine which individuals are likely to develop heart disease, but researchers have now validated an even better test, called thallium screening. Patients with documented premature heart disease and their healthy siblings underwent a standard treadmill exercise ECG and were also injected with thallium, a radioactive substance. The subjects' hearts were then scanned with a camera that detects radioactivity to determine if any narrow or blocked blood vessels were present. During follow-up over an average of six years, some individuals developed clinical signs of heart disease, including heart attacks. The data showed that thallium screening predicts coronary heart disease better than exercise ECG alone, particularly in high-risk asymptomatic individuals. These include men over age 45, as well as younger male and older female siblings of heart disease patients.

Breast cancer kills more than 45,000 women every year in the United States. Those with advanced breast cancer have a particularly low chance of survival. High dose chemotherapy and bone marrow transplantation may cause long-term remission in some women, but most relapse following these treatments. Researchers at a General Clinical Research Center are now exploring radioimmunotherapy as an option to treat advanced breast cancer. In this type of therapy, antibodies to tumor cells are combined with a radioisotope bound to a specific antibody and injected into a patient. The antibodies then carry the radioisotope throughout the body, where radiation acts to kill cancerous cells. Because of the antibody targeting, the tumors receive greater amounts of radiation than healthy organs. The 50% rate of response to radioimmunotherapy is encouraging and, when combined with other treatments such as chemotherapy, may improve a woman's chance of surviving breast cancer.

Revolutionary imaging technologies, together with new techniques, have advanced scientists' ability to penetrate the intricate structural organizations in living beings safely and noninvasively. Using a magnetic resonance imaging (MRI) technique, researchers at the University of New Mexico GCRC have developed a dependable, noninvasive means to reliably visualize tiny nerves

visualize tiny nerves in the lower leg of diabetics and normal control patients to evaluate nerve damage. Damaged nerves signal severe or poorly controlled diabetes. The capacity to quantify changes in the characteristics of the nerves and measure the degree of damage will allow physicians to rapidly and safely evaluate a patient's neuropathy and determine its progression or improvement in response to treatment.

Gene therapy is among the fastest growing and most promising areas of research, with unparalleled potential for preventing many common and rare diseases and disorders, and for reducing the costs of health care in the future. NCRR's GCRCs are the principal sites of much of the clinical genetic research ongoing in the United States for gene therapy of single and multi-gene disorders. To enhance the capacity of clinical investigators to proceed with gene therapy, NCRR--together with the National Cancer Institute, National Heart, Lung, and Blood Institute, and National Institute of Diabetes and Digestive and Kidney Diseases--has funded three national Gene Vector Laboratories. These shared resources will facilitate the production of vehicles designed to deliver genetic material into human somatic cells for the prevention, treatment, and cure of a wide variety of medical conditions through human gene therapy. In FY 1997 this initiative will continue, and will also include studies of gene vectors in animal models.

Biomedical Models

NCRR supports a network of seven Regional Primate Research Centers (RPRCs) and develops other shared resources that provide biomedical investigators with a broad range of research models, from non-human primates to mathematical and other non-animal models of disease. NCRR also supports development of an array of unique animal models, including transgenic and knock-out animal models, as well as worms and marine species, for research on a broad range of health problems.

Scientists at the New England Regional Primate Research Center have identified a new target in the brain for medications to treat cocaine addiction. Using a nonhuman primate model, the scientists explored how cocaine interacts with the brain to alter behavior and induce dependence. Cocaine is known to interfere with a number of chemical messengers in the brain, called neurotransmitters, and previous research points to one specific transmitter, dopamine, as the primary target. The current study suggests that, in addition to the dopamine system, brain norepinephrine systems might also be involved, which may facilitate the development of effective drug treatments for cocaine addiction.

Recent studies of nonhuman primates at the Yerkes Regional Primate Research Center suggest that drugs that alter brain serotonin levels may reduce the risk of relapse in individuals who are trying to abstain from cocaine, particularly after long-term, frequent use. Relapse is a major obstacle to overcoming cocaine addiction. However, if relapse occurs during treatment with medications that boost brain serotonin activity, the data suggest that this intervention could reduce the euphoric effects of cocaine--which is necessary for a treatment to succeed with chronic users.

Vitamin A is a naturally-occurring, essential nutrient for normal cellular function—including reproduction and development. However, there is growing concern that ingestion of excess vitamin A supplements during pregnancy may be associated with birth defects, and it is yet to be established how much vitamin A pregnant women may safely take. Recent studies of cynomolgus monkeys, however, revealed important new information linking birth defects with excessive doses of vitamin A during early pregnancy. Results show a dose-related increase in birth defects involving the craniofacial region, heart, and thymus gland. These studies have demonstrated that the teratogenic threshold dose of vitamin A in the monkey model is 20,000 IU/kg, which is more than 100 times the recommended level for pregnant women.

The best way to treat infants born with respiratory distress syndrome (RDS) is to evenly distribute throughout the lung a substance known as surfactant that normally coats the inner lining of the lung and prevents it from collapsing during exhalation. Studies assessing the efficacy and safety of a synthetic peptide-phospholipid (KL4) surfactant are being conducted on premature, infant rhesus monkeys at the California RPRC. By monitoring the acute effects on cardiopulmonary status, compliance, and improvements in arterial/alveolar oxygen tensions, the investigators have established that these surfactants are effective and safe for nonhuman primates. These experiments have provided the impetus for proceeding to controlled clinical trials in human infants.

Biomedical Technology Resources

Access to advanced NCRR technologies is critical to the rapid progress of biomedical research. NCRR funds two peer-reviewed programs to achieve this goal. The first consists of a national network of shared biomedical technology centers that research and develop new and innovative technologies. These are shared with thousands of NIH-supported investigators through collaborative and service projects. The second program funds the purchase of very expensive and commercially available state-of-the-art instrumentation that is shared by an average of 15 investigators whose work is supported primarily by NIH research grants.

Scientists at the Resource for Magnetic Resonance of the University of Pennsylvania are also using high resolution Magnetic Resonance Imaging (MRI) to detect and characterize breast cancer to improve the care of breast cancer patients. Their research in ultra-high resolution breast MRI indicates that architectural findings on post-contrast breast MRI are highly predictive of benign and malignant breast lesions. Investigators found that approximately 70% of benign breast biopsies can be avoided by using high resolution MRI analysis without sacrificing detection of cancer.

Pathogenic bacteria are responsible for many infectious diseases including gonorrhea and meningitis. To date, vaccines for gonorrhea have failed largely because the fiber-forming protein, pilin, produced by the bacterium changes rapidly. Understanding how the pilin molecule adheres to cells could lead to the development of vaccines or new therapeutic agents to prevent infection by these bacteria. The pilin protein structure from gonorrhea has been determined using an NCRR high-energy synchrotron radiation resource, which allows researchers to see very small crystals. Researchers can now identify the cell region changes which are necessary for

infection and important for understanding the basis of drug resistance that occurs with gonorrhea. Research explaining cell region changes could lead to systematic drug therapy to prevent gonorrhea and other infectious diseases.

Tuberculosis infects one-third of humanity and is one of the world's most threatening diseases. The ability of *Mycobacterium tuberculosis* to cause infection is closely linked to its capacity to acquire iron from its host. However, free iron is very limited in humans and this mycobacterium has developed high-affinity iron-binding molecules, called exochelins, which can remove iron from host iron-binding proteins. Researchers at the University of California (UC), Los Angeles, in collaboration with the NCRR-supported Mass Spectrometry Research Resource Center at the UC, San Francisco, have determined the structure of these exochelin molecules. This will provide information crucial to the design of novel antibacterial therapeutics.

The most efficient way to transfer recombinant genes into somatic cells for gene therapy is to use viruses as the vehicle. However, the use of certain viruses, such as adenovirus, induces a lymphocyte-mediated immune response in the patient that not only results in a loss of the gene's function, but also induces inflammation in the target organ. A state-of-the-art cell sorter, purchased with funds from a Shared Instrumentation Grant, has enabled investigators to devise ways to counter these problems. This instrument separates lymphocytes into classes based on their function and in quantities much greater than had been achievable by traditional methods. This approach has demonstrated that a single class of lymphocytes is responsible for eliminating the gene-containing cells from the patient's body. Further studies will aid in the design of rational strategies to overcome immunological barriers to gene therapy.

RESEARCH INFRASTRUCTURE

The NCRR's Research Infrastructure activities address the underrepresentation of minority investigators and enhance the research environment at minority colleges and universities that award doctoral degrees in health sciences. In addition, NCRR improves biomedical and behavioral research facilities through matching grants to assist in the construction and rehabilitation of the Nation's basic and clinical, biomedical, and behavioral research facilities. Because minority Americans are severely underrepresented in scientific and health fields at every level, NCRR supports programs that increase the pool of minority high school students interested in science careers, enhance K-12 science teacher education and skills, and improve pre-college science education and the public's understanding of science.

Institutional Development

The objective of the Research Centers in Minority Institutions (RCMI) program is to expand the national capacity for research in the health sciences. Recipient institutions use RCMI funds to hire additional research faculty in the biomedical and behavioral sciences, support training in specialized analytical methods, upgrade facilities, purchase advanced scientific instrumentation and conduct developmental and collaborative research projects.

For example, lymphocyte mitogenic assays play a very important role in clinical immunology. These assays are used singly or in combination with other methods to quantify the cellular immune competence of patients. Now, researchers at Ponce School of Medicine in Puerto Rico have developed a new flow cytometric method to quantitatively assess lymphocyte proliferation simultaneously for different subsets. This new method is more informative than conventional mitogenic assays and should be invaluable for studying the nature and extent of interactions between different cellular subsets within a culture. This non-radioactive alternative also promises more accurate interpretation of results which now could be strongly biased when the responses of subsets significantly differ from each other.

In FY 1995, the RCMCI Clinical Research Infrastructure Initiative was implemented to provide support for expansion and development of clinical faculty, specialized facilities, and core laboratories for clinical research, and for clinical research protocols and projects. These resources should facilitate increased participation in clinical trials and foster collaborations with the General Clinical Research Centers. Also in FY 1995 the NCRR initiated a program to develop biomedical research infrastructure at minority institutions offering baccalaureate or master's degrees in health-related fields.

The NCRR also supports Institutional Development Awards to provide infrastructure support to institutions in states with historically lower levels of NIH competitive research funding. The primary goal of this program is to enhance the competitiveness of research institutions in eligible states and thus broaden the geographical distribution of NIH funding for biomedical research.

Science Education

Minority Americans are severely underrepresented in scientific and health fields at every level, and it is generally agreed that the long-term solution is to improve the early science education of minority youth. The increasing number of occupations that require a knowledge of scientific principles and the predicted increase in the minority population make it imperative that pre-college education help minority youth become more productive and competitive. The NCRR's K-12 Teachers and High School Students (K-12) program is designed to increase the pool of underrepresented minority high school students who are interested in pursuing health careers, and are academically prepared to enter college. The K-12 program provides salary support for teachers and minority high school students while they obtain structured science research experience in health research laboratories. This allows teachers to keep pace with the explosive growth of scientific knowledge in health-related areas and pass it on to their students, and provides students hands-on exposure to health-related research to stimulate their interest in careers in the health sciences.

The main objective of the Science Education Partnership Award (SEPA) program is to encourage university-based scientists to work with educators and other organizations to improve student and public understanding of health-related science. The program began in FY 1991 with awards to develop a broad range of model programs, including a national video education program, a traveling AIDS exhibit, biotechnology research experiences for students and teachers, and health promotion outreach for inner city and rural communities. Expansion of the program in

in FY 1994 was designed to support validation of the most promising model systems, as well as to promote dissemination of well-tested programs to larger audiences. The goal is to increase students' understanding of science and the public's science literacy in the biomedical and behavioral sciences. The availability of new long distance learning technologies should lead to dissemination of these health-related science education programs on a regional or national scale.

One example of a successful SEPA model system is CityLab, a biotechnology learning laboratory for teachers and high school and middle school students at Boston University School of Medicine. Student participation has increased to more than 3,300 in FY 1994, and more than 500 teachers have attended workshops. The program provides access to state-of-the-art facilities and curricula otherwise unavailable to most school systems. Students are challenged to solve problems, presented in a mystery format, using the latest techniques and concepts of genetics and molecular biology. Dissemination of this science education model is proceeding well. In response to overwhelming demand, a second laboratory has opened, and satellites are being instituted throughout New England. Inquiries for establishing satellites have been received from as far away as Alaska. The long-term goal is to have a network of CityLab sites around the country.

Research Facilities

The NCRR provides matching grants to assist in the construction and rehabilitation of the Nation's basic and clinical biomedical and behavioral research facilities. This initiative began in FY 1994 in response to Congressional recognition of a growing deficit in satisfactory research space that significantly threatens progress in biomedical research, and of a need to replace outmoded facilities, relieve overcrowding, and accommodate changing research requirements. Institutions of emerging excellence and Regional Primate Research Centers were identified as having particular needs; in addition, several research areas warranted encouragement because of changing research requirements. No funds are requested for this program in FY 1997, reflecting the higher NIH priority for research project grants. The NCRR also provides funds for the alteration and renovation of animal resources, and the purchase of major equipment related to these resources.

Future Program Directions

Clinical Research Resources

NCRR provides a national network of General Clinical Research Centers (GCRCs) with facilities that extend the research capabilities of NIH-supported investigators. NCRR's capacity to continue supporting these GCRCs and providing facilities designed to meet today's biomedical research needs hinges largely on its capacity to maintain and enhance these resources. In turn, the effectiveness of the centers determines the status of continued meritorious research projects and novel pilot studies.

Over the past decade, outpatient studies at these clinical research centers have gradually increased. To complement this trend and provide easy access to people who participate in clinical studies, GCRCs need to reconfigure their units and personnel assignments. Also, by funding satellite GCRCs in specialty or pediatric hospitals, the centers can diversify patient groups in terms of ethnic origin, age, and disease categories.

Clinical research holds great promise for understanding and treating disease, but requires facilities and laboratories that not only meet the needs of researchers, but also the requirements of the Food and Drug Administration for good manufacturing practices, including stringent quality control. For example, new research areas, such as cellular and immunomodulated therapies and gene therapy trials, require appropriate facilities and laboratories for clinical grade product preparation.

In addition to ensuring modern, clinical research environments, NCRR's GCRC program supports clinical research training and career development for physicians, with special emphasis on career enhancement for minority physicians. To reverse the decline of the number of physician investigators submitting new NIH grant applications and to increase the numbers of individuals pursuing careers in patient-oriented clinical research, NCRR will continue to support its Clinical Associate Physician programs and Clinical Scholars program that offer young physicians intensive training in the basics of clinical research. Also, established investigators and physicians in training will be offered formalized patient-oriented research courses and hands-on training in selected novel technologies at GCRCs.

Shared/Advanced Technologies

NCRR funding provides the scientific community with a national network of about five dozen biomedical technology resource centers. Here, research and development leads to innovative technologies and instrumentation that can be shared by NIH-supported investigators. The demand for user access to these resource centers has increased enormously. For example, in the past decade, synchrotron radiation—which enables scientists to study the three-dimensional structure of proteins, nucleic acids, and viruses—has made impressive contributions to biophysical research. But the number of synchrotrons and current funding levels cannot keep pace with the demand, and still preserve time for resource staff to conduct research on new technology development. Further, there is little flexibility to support work on very difficult, time-intensive problems. To alleviate this problem, NCRR is supporting the construction of two additional synchrotron beam lines at the Advanced Photon Source, a Department of Energy synchrotron facility at the Argonne National Laboratory in Illinois.

The development of unprecedented communications networks—next-generation Internet interfaces, virtual environments, and other visualization technologies—holds great promise for future "laboratories without walls." Accordingly, in FY 1997 NCRR plans to solicit research applications to establish a collaborative test bed to address problems related to structural biology research. This collaborative effort will foster development of effective tools for sharing software and data, controlling use of remote instruments, and communicating with colleagues at distant sites. Interactive, real-time magnetic resonance imaging (MRI), for example, can now be done

on the World Wide Web by using state-of-the-art instrumentation. With universally available browser software, researchers anywhere soon will be able to access simple on-screen instructions that allow them to review and modify experimental conditions or observations in an MRI system.

Biomedical Models

Existing facilities in the nationwide network of seven Regional Primate Research Centers (RPRCs) are more than 30 years old and require upgrading and/or replacement. In addition, biosafety requirements for studies of infectious diseases require specialized facilities. Four of the RPRCs have already begun work in gene therapy, and two have work underway in related areas such as micro injection into individual cells, embryonic and other stem cells as vectors for delivering specified genes.

Future activities will include a workshop to address problems identified by the 1995 special NIH Panel report on gene therapy and to determine how the non-human primate models can best be used. Basic research using the non-human primate will examine gene transfer vectors, in order to better understand the biological interactions of these vectors within the host, disease pathophysiology, and potential clinical efficacy.

To ensure future availability of chimpanzees and other animal models, basic research on the cryopreservation of gametes and embryos is needed. NCRR also needs to develop national resources of genetic stocks of animals for the biomedical community, including transgenic and knockout animals, and the cryopreservation of embryos and spermatozoa of mice, rats, rabbits, and other species.

NCRR is also studying cryopreservation of genetic lines that will eventually enable less costly animal facilities. For example, a method for extending the lifetime of sea urchin eggs will expand the types of experiments that can be done on this animal model. A transgenic zebrafish model can be used in environmental toxicology and mutational analyses. This model will also aid the Human Genome Project by developing faster technology for understanding how genetic alterations affect embryological development and disease. NCRR plans to develop several Interdisciplinary Resource Centers. Each center will focus on a single organism and develop expertise for generating inbred lines and transgenic animals, cryopreserved material, and a data base for use by the research community.

Infrastructure

NCRR has long sought to improve the underrepresentation of minority investigators and enhance the research environment at minority colleges and universities that award doctoral degrees in the health sciences. A new NCRR program, co-sponsored by NCRR and NIH's Office of Research on Minority Health, is directed at helping minority institutions that do not award doctoral degrees more effectively compete for research funding. Stronger collaborative relationships between these minority institutions and research-intensive universities will help increase the involvement of minority institutions in biomedical research and the number of minority students seeking advanced degrees in the biomedical sciences.

NCRR also funds a program to enhance science teacher education and skills and improve pre-college science education and the public's understanding of science. Because there are several promising projects now in the dissemination phase, it is critical to continue this program at some level to support high-quality innovative science education projects.

In conclusion, the shared resources and biomaterials that NCRR offers the research community stimulate cost savings and provide opportunities for major medical discoveries that improve human health. The challenge now is to continue building a research infrastructure that can adapt to today's realities and tomorrow's opportunities.

NATIONAL INSTITUTES OF HEALTH

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BUDGET MECHANISM

	1995		1996		1997	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting.....	49	\$9,915,000	64	\$13,557,000	94	\$18,777,000
Admin. suppl.....	(4)	74,000				
Competing.....						
Renewal.....	11	2,793,000	15	2,430,000	18	2,916,000
New.....	26	4,332,000	41	6,448,000	46	7,312,000
Supplemental.....						
Subtotal competing.....	37	7,125,000	56	8,878,000	64	10,228,000
SBIR/STTR.....	31	6,028,000	70	8,436,000	70	8,436,000
Subtotal, res. proj.....	117	23,142,000	190	30,871,000	228	37,441,000
Research Centers:						
Clinical research.....	78	104,333,000	76	113,834,000	76	115,084,000
Biomedical research technology..	62	46,832,000	62	46,888,000	62	47,688,000
Comparative medicine/						
biological models and materials....	29	34,164,000	30	35,080,000	30	35,480,000
Research centers in minority institutions...	17	20,692,000	19	22,599,000	19	22,599,000
Subtotal, research centers....	186	206,021,000	187	218,201,000	187	220,851,000
Other research:						
Research career programs.....	18	1,327,000	14	1,001,000	14	1,001,000
Biomedical research support.....	120	16,548,000	190	23,255,000	174	22,445,000
Other research related.....	38	9,072,000	52	9,842,000	44	8,842,000
Subtotal, other research.....	176	26,947,000	256	34,098,000	232	32,288,000
Total, research grants.....	479	256,110,000	633	283,170,000	647	290,580,000
Training:						
Individual awards:						
Noncompeting.....	1	16,000	1	16,000	3	105,000
Competing.....			3	107,000	1	18,000
Subtotal, individual.....	1	16,000	4	123,000	4	123,000
Institutional awards:						
Noncompeting.....	54	1,945,000	72	2,585,000	68	2,489,000
Competing.....	23	763,000			4	146,000
Subtotal, institutional.....	77	2,708,000	72	2,585,000	72	2,635,000
Total, training.....	78	2,724,000	76	2,708,000	76	2,758,000
Research and development contracts..	7	4,300,000	7	3,076,000	7	2,991,000
(SBIR/STTR).....	(2)	(411,000)				
Construction.....		9,963,000		20,000,000		
Research management and support.....	FTEs		FTEs		FTEs	
	98	14,244,000	96	13,015,000	96	13,015,000
Total.....	98	287,341,000	96	321,969,000	96	309,344,000
Clinical Trials.....		(35,591,000)		(38,724,000)		(39,148,000)

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Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTE	Amount	FTE	Actual 1/ Amount	FTE	Amount	FTE	Estimate	FTE	Estimate	FTE	Amount
Extramural Research:												
Shared resources.....	--	\$211,389	--	\$215,683	--	\$227,468	--	\$253,524	--	\$262,709	--	+9,185
Research infrastructure..	--	37,464	--	42,380	--	45,612	--	55,430	--	33,620	--	-21,810
Subtotal, extramural....	--	248,853	--	258,063	--	273,080	--	308,954	--	296,329	--	-12,625
Research management and support.....	108	12,901	98	12,456	98	14,213	96	13,015	96	13,015	--	0
Subtotal, obligations...	108	261,754	98	270,519	98	287,293	96	321,969	96	309,344	0	-12,625
Unobligated balance lapsing.....	--	22	--	13	--	48	--	--	--	--	--	0
Total budget authority.....	108	261,776	98	270,532	98	287,341	96	321,969	96	309,344	0	-12,625

1/ Excludes an emergency supplemental of \$1,000,000 transferred from OASH for earthquake relief.

Note: Includes FTEs associated with HIV activities. Funds to support these activities are included in the NIH Office of AIDS Research.

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Summary of Changes

1996 Estimated budget authority.....	\$321,969,000
1997 Estimated budget authority.....	309,344,000
Net Change.....	-12,625,000

	1996		Change from Base	
	Estimate Base	Budget	Change from Base	Budget
	(FTES)	Authority	(FTES)	Authority
Changes:				
A. Built-in:				
1. Research Management & Support				
a. Within grade increases.....		\$5,079,000		+\$88,000
b. Annualization of 1996 pay raise.....		5,079,000		+32,000
c. 1997 pay increases.....		5,079,000		+113,000
d. Federal Employees Compensation Fund....		29,000		+2,000
e. DHHS Working Capital Fund....		123,000		
f. Payment for Centrally Furnished Services		4,142,000		-370,000
g. Service & Supply Fund.....		1,326,000		+46,000
h. Increased costs of supplies and materials		2,450,000		+89,000
Subtotal.....				0
B. Program:				
	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.....	64	13,557,000	30	+5,220,000
b. Competing.....	56	8,878,000	8	+1,350,000
c. SBIR/STTR.....	70	8,436,000		
Total.....	190	30,871,000	38	+6,570,000
2. Research centers.....	187	218,201,000		+2,650,000
3. Other Research.....	256	34,098,000	-24	-1,810,000
4. Research Training.....	76	2,708,000		+50,000
5. Research & Development Contracts	7	3,076,000		-85,000
6. Facilities Construction.....		20,000,000		-20,000,000
	(FTES)		(FTES)	
7. Research Management and Support.	96	13,015		
Subtotal.....				-12,625,000
Total changes.....				-12,625,000

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Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable work years: Full-time equivalent employment.....	85	85	---
Full-time equivalent of overtime and holiday Hours.....	---	---	---
Average ES salary.....	\$104,000	\$104,000	---
Average GM/GS grade.....	9.7	9.8	---
Average GM/GS salary.....	\$34,696	\$36,729	+\$2,033
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)...	\$77,607	\$77,607	---
Personnel compensation:			
Full-time permanent.....	\$3,936,000	\$4,118,000	+\$182,000
Other than full-time permanent.....	193,000	202,000	+9,000
Other personnel compensation.....	150,000	159,000	+9,000
Total, personnel compensation.....	4,279,000	4,479,000	+200,000
Personnel benefits.....	768,000	803,000	+35,000
Benefits for former personnel.....	32,000	32,000	---
Travel and transportation of persons.....	83,000	83,000	---
Transportation of things.....	17,000	17,000	---
Rent, communications, and utilities.....	473,000	473,000	---
Printing and reproduction.....	111,000	111,000	---
Other services:	470,000	470,000	---
Consultant services.....			
Other Services.....	278,000	278,000	---
Purchase from Govt. Accts.....	7,111,000	6,876,000	-235,000
R&D Contracts.....	2,276,000	2,191,000	-85,000
Supplies and materials.....	52,000	52,000	---
Equipment.....	106,000	106,000	---
Grants, subsidies & contributions.....	305,878,000	293,338,000	-12,540,000
Unemployment comp. & insurance.....	35,000	35,000	---
Total.....	\$321,969,000	\$309,344,000	\$-12,625,000

NATIONAL INSTITUTES OF HEALTH
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Administrative Costs

	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>	<u>Change</u>
Personnel Compensation:			
Full-time Permanent (11.1).....	\$3,936,000	\$4,118,000	+\$182,000
Other than Full-time Permanent (11.3) ..	193,000	202,000	+9,000
Other Personnel Compensation (11.5)....	<u>150,000</u>	<u>159,000</u>	<u>+9,000</u>
Total Personnel Compensation(11.9)...	4,279,000	4,479,000	+200,000
Civilian Personnel Benefits.....	768,000	803,000	+35,000
Benefits to Former Personnel (13.0).....	32,000	32,000	—
Travel (21.0).....	83,000	83,000	—
Transportation of Things (22.0).....	17,000	17,000	—
Communications, Utilities, and Miscellaneous Charges (23.3).....	473,000	473,000	—
Printing and Reproduction (24.0).....	111,000	111,000	—
Consulting Services (25.1).....	20,000	20,000	—
Other Services (25.2).....	78,000	78,000	—
Purchases from Govt. Accts. (25.3).....	4,342,000	4,315,000	-27,000
Operation of GOCOs (25.4).....	—	—	—
Operation of Equipment (25.7).....	200,000	200,000	—
Supplies and Materials (26.0).....	<u>52,000</u>	<u>52,000</u>	<u>—</u>
Total.....	10,455,000	10,663,000	+208,000

NATIONAL INSTITUTES OF HEALTH

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SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Primate Centers -- The House in its report 104-209, page 76, states its understanding that primate center grants are competitively awarded. The Committee urges NCRR to make clear to any institutions not currently receiving primate center grants that they are permitted and encouraged to apply for center funding as current grants expire. The committee intends that NCRR will announce the opportunity to apply for primate center funding in the NIH Guide for Grants and Contracts as the current grants come up for renewal.

Action Taken or to be Taken

Currently, the competition for a Regional Primate Research Center (RPRC) is open. However, the seven RPRCs presently in operation were established over 30 years ago with several million dollar investments in land, buildings, equipment and large numbers of nonhuman primates. Given the ban on importation of most of the nonhuman primates, coupled with the current economic climate, it would be difficult for another institution to provide the necessary infrastructure, specialized personnel, sufficient numbers of investigators with appropriate expertise to work collaboratively with other investigators from other universities around the country, and sufficient animal numbers for the establishment of a RPRC. The NCRR does, however, have an existing program for development of centers which support animal research for nonhuman primates. This program is re-announced annually, and applicants will be encouraged to utilize this program for the development and support of their nonhuman primate facilities.

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Authorizing Legislation

	PHS ACT/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Estimate
Research and Investigation.....	Section 301	42s241	Indefinite	\$319,261,000	Indefinite	\$306,586,000
National Center for Research Resources.....	Section 479, 480	42s287 287a, 300a, and 5s332	Such sums as necessary		Such sums as necessary	
National Research Services Awards.....	Section 487		Such sums as necessary	2,708,000	Pending authorization	2,758,000
Total Budget Authority.....				321,969,000		309,344,000

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation ^{1/}
1988	\$280,415,000	\$346,652,000 ^{2/}	\$367,415,000	\$368,153,000
1989	319,977,000 ^{3/}	355,767,000 ^{4/}	367,987,000	358,608,000 ^{5/}
1990	263,313,000 ^{6/}	356,128,000	362,253,000	353,734,000 ^{7/}
1991	319,151,000	355,962,000	331,629,000	335,255,000 ^{8/}
1991	Sequester			(4,000)
1992	320,975,000	309,200,000	317,227,000	314,213,000 ^{9/}
1993	330,231,000	311,207,000	315,551,000	312,468,000 ^{10/}
1994	327,887,000	328,915,000	332,915,000	331,915,000
1995 ^{11/}	286,394,000	294,824,000	294,824,000	294,737,000 ^{12/}
1995	Rescission - 1,000,000			
1996 ^{11/}	316,544,000	321,969,000	304,267,000	321,969,000
1997 ^{11/}	309,344,000			

^{1/} Reflects enacted supplementals, rescissions, and reappropriations.

^{2/} Does not include funding for AIDS research which was consolidated at the Secretary's level.

^{3/} The 1989 request excludes funds for AIDS research and education (\$38,010,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

^{4/} Excludes \$2,220,000 in NRSA training programs not considered.

^{5/} Reflects a 1.2% reduction (\$4,356,000) and a reduction of \$23,000 as a result of improved procurement practices from the appropriated level of \$362,987,000 as required by P.L. 100-436 Sections 517 and 215 respectively.

^{6/} The 1990 request excludes funds for the National HIV program (\$44,643,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

^{7/} Excludes enacted administrative reductions of \$16,000 for procurement savings; \$344,000 for extramural salary cap and \$97,000 for salaries and expenses.

^{8/} Excludes enacted administrative reduction of \$8,541,000.

^{9/} Includes enacted administration reduction of \$669,000, and enacted rescission of \$338,000.

^{10/} Reflects a .8% reduction (\$2,522,000), a S&E reduction (\$235,000), and Consultant Services reduction (\$26,000).

^{11/} Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995, FY 1996 and FY 1997.

^{12/} Excludes enacted administrative reductions of \$57,000, \$23,000 and \$60,000.

National Center for Research Resources

Detail of Full-Time Equivalent Employment (FTE)

	1995	1996	1997
	<u>Actual</u>	<u>Estimate</u>	<u>Estimate</u>
Office of the Director.....	5	5	5
Office of Administration.....	22	22	22
Office of Extramural Activities.....	31	29	29
Office of Science Policy.....	10	9	9
Clinical Research	9	9	9
Comparative Medicine.....	8	8	8
Biotechnology.....	7	7	7
Research Infrastructure.....	6	7	7
Biomedical Engineering & Instrumentation.....	0	0	0
Library.....	0	0	0
Medical Arts & Photography.....	0	0	0
Veterinary Resources.....	0	0	0
Total, NCRR	98	96	96

Average GS Grade

1992.....	9.9
1993.....	9.8
1994.....	10.1
1995.....	9.7
1996.....	9.7
1997.....	9.8

Program Administration
Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Request
Executive level I	0	0	0
Executive level II	0	0	0
Executive level III	0	0	0
Executive level IV	0	0	0
Executive level V	0	0	0
Subtotal	0	0	0
ES-6	0	0	0
ES-5	1	1	1
ES-4	1	1	1
ES-3	0	0	0
ES-2	0	0	0
ES-1	1	1	1
Subtotal	3	3	3
GS-15	9	9	9
GS-14	13	13	13
GS-13	8	7	7
GS-12	8	9	9
GS-11	7	6	7
GS-10	0	0	0
GS-9	4	5	6
GS-8	6	5	5
GS-7	13	14	12
GS-6	6	6	6
GS-5	6	5	6
GS-4	0	2	1
GS-3	1	0	0
GS-2	0	0	0
GS-1	0	0	0
Subtotal	81	81	81
Grades Established by Act of July 1, 1994 (42 U.S.C. 207):			
Assistant Surgeon General	2	2	2
Director Grade	0	0	0
Senior Grade	0	0	0
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	2	2	2
Ungraded			
Total permanent positions	86	86	86
Total positions, end of year	98	96	96
Total full - time equivalent employment, end of year	98	96	96
Average ES level	3.3	3.3	3.3
Average ES salary	\$104,000	\$104,000	\$104,000
Average GS grade	9.7	9.7	9.8
Average GS salary	\$34,015	\$34,696	\$36,729



WEDNESDAY, APRIL 24, 1996.

NATIONAL LIBRARY OF MEDICINE

WITNESSES

DONALD A.B. LINDBERG, M.D., DIRECTOR, NATIONAL LIBRARY OF MEDICINE

KENT A. SMITH, DEPUTY DIRECTOR

SUSAN U. LEVINE, BUDGET OFFICER

DONALD C. POPPKE, EXECUTIVE OFFICER

MELVIN L. SPANN, ASSOCIATE DIRECTOR, SPECIALIZED INFORMATION SERVICES

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. Next, we consider the budget of the National Library of Medicine. We're pleased to welcome Dr. Donald Lindberg, the Director. Dr. Lindberg, nice to see you.

OPENING STATEMENT

Dr. LINDBERG. Thank you, Mr. Chairman. It is a privilege and a pleasure to appear before you today. I am pleased to report that the NLM is making good progress in ensuring that all American health professionals—those who treat patients, who conduct research, and who educate students—have rapid and reliable information services. My formal statement submitted for the record emphasizes our familiar work—the robustness of the Library's collection and online services, the remarkable growth of the GenBank database of molecular sequences, and the success of medical librarians and the national network of Libraries of Medicine in 4,500 cities and towns providing medical information services to medical professionals and to the public.

Today, with the help of three very short video clips, I want to tell you about some of the new efforts in the past year. First, the Visible Human Project. This has resulted in two complete three dimensional computer-stored human bodies, a male and a female. The Visible Human Male, introduced late in 1994, consists of magnetic resonance images, CAT scans, and anatomic images from a single male cadaver. It is about 14 billion bites in size and available on the Internet for teaching and for research. A database of the Visible Human Female was introduced just last November. It is like the male, except that the imagining was done to a much finer level of detail. It is about 40 billion bites in size. I would like to show you a video clip of the project. It is just a minute.

[Video presentation.]

INTRODUCTION OF WITNESSES

Dr. LINDBERG. Mr. Porter, in my eagerness to get started, I deviated from the usual plan to introduce my colleagues. Perhaps you'll permit me to do so now and introduce Dr. Mel Spann, at the far end of the table, he is Associate Director of the Library and also the head of the Specialized Information Services Division; next is Mr. Don Poppke, our good Executive Officer; Sue Levine, our Budget Officer; and Mr. Kent Smith, our Deputy Director. You know Dr. Varmus, and Mr. Williams.

OPENING STATEMENT

If you will permit me to go on, next I would like to tell you about a telemedicine activity. There is a special excitement these days about projects that involve telemedicine. We see it as having a great potential for improving the quality of health care, especially where remoteness of patient and provider is a factor. The NLM is funding a number of geographically dispersed telemedicine-related projects in such areas as radiology, neurology, dermatology, and rural medicine. In this last category, I would like to show you a very brief video clip from our West Virginia Project.

[Video presentation.]

Dr. LINDBERG. As important as such testbed projects are, there is also a great need to obtain evaluations of the actual and potential benefits of these telemedicine services to real patients and to the health care system. To accomplish this, the Library is funding a study by the Institute of Medicine to develop criteria for evaluating telemedicine work, based, in part, on site visits to our actual telemedicine grant sites. The National Library of Medicine is also co-funding a study by the National Research Council on how best to ensure the confidentiality of electronic patient records while providing effective access during the telemedicine encounters.

Mr. Chairman and members of the committee, the first two projects you have just seen, the Visible Human and Telemedicine, may be described as experimental. Their ultimate payoff for the Nation is in the future, although I would say in the near future. The third project, and the last, I wish to describe to you is here and now; this is Internet Grateful Med. Members of the committee may perhaps recall that Grateful Med is the software that permits anyone with a personal computer and a modem to search NLM's MEDLINE and our other databases. Over 7 million searches of this sort were done on the database last year, most of them via the Grateful Med software. We know that about half were done specifically to treat individual patients and the other half for research and education.

Just last week, we announced a new and improved version, quite a radically improved version, of Grateful Med for those who have access to Internet and to the World Wide Web. The last video clip I am going to show is about a minute from the TV coverage of last week's announcement. I should say that in this case we're grateful to the Congress of the United States not only for the funding but for the video talent.

[Video presentation.]

Dr. LINDBERG. Yes, that's sort of a fun one. As we look to the future, we believe that in addition to health professionals, the public too will demand even greater access to health information. The Library has already begun a modest shift towards satisfying the information needs of the general public, especially in the areas of toxicology and environmental health, HIV/AIDS, and, most recently, clinical practice guidelines for patients.

The success of NLM's outreach efforts has increased the demand for its basic library services—acquiring, preserving, and providing access to books, journals, and other pertinent materials. As we continue to develop new health information programs for the country's National Information Infrastructure, we must be mindful they are in many cases founded and dependent upon traditional library practices. Hence, we are grateful to this committee and to the Congress for their generous and sustained support of NLM's basic services as well as our funding for the exciting new services.

The President's request for NLM for fiscal year 1997 is \$143,268,000. I thank you, and I will be glad to try to answer any of your questions.

[The prepared statement and biography of Dr. Donald Lindberg follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Library of Medicine

Mr. Chairman, thank you for the opportunity to appear before you today. I am pleased to report that the National Library of Medicine is making remarkable progress in ensuring that all American health professionals--those who treat patients, conduct research, and educate students--have rapid and reliable information services available to them.

The reliability of these computerized information services was demonstrated in a striking manner during the recent furlough and the following blizzard. We essentially put our online databases on "automatic pilot," and hoped that a very small staff could keep them up around the clock. I am proud to say that we maintained online services to our network of 135,000 users without missing a beat.

Some 7.3 million searches were done on the NLM online databases last year. We know that about half were done specifically to treat patients, the other half by scientists and for education and training. Our users conduct the vast majority of their searches in professional anonymity--from personal computers in offices, laboratories, and classrooms. Occasionally, however, they share with us a particularly memorable story about their use of MEDLINE, our largest database. I would like to share with you an unusual anecdote we received by letter in 1995 that demonstrates the value of online searching.

A pharmacist from Maryland told how Grateful Med led her directly to information that helped her and her husband find the appropriate treatment that resulted in a successful pregnancy and birth of a healthy son. Grateful Med is the software used most often by those wishing to search NLM's MEDLINE database. She concluded her letter: "To everyone responsible for Grateful Med, we would just like to let you know that our family will be eternally 'Grateful' for Sam."

There are many uses of MEDLINE and other NLM databases in the nonclinical arena, for example: the scientist whose search of the literature provides a clue that leads to an experiment that extends our knowledge about how to treat disease; a firefighter responding to a chemical spill whose search at the scene using a portable terminal pinpoints data about how to handle the mix of dangerous chemicals; the librarian who downloads new book cataloging records from the NLM, thus making unnecessary expensive local cataloging; the group of citizens who use a database on NLM's network to discover more about hazardous substances being released by industry into the local environment; and the concerned parent who uses MEDLINE to learn where the latest research about a rare childhood illness is being conducted.

Although MEDLINE is the largest of the NLM online files, there is a series of other databases in such specialized areas as cancer, AIDS, and environmental health. A number of these files contain data that

may be used directly by the general public, for example, the "PDQ" file of cancer treatment information and the Toxic Chemical Release Inventory databases that contain extensive data--by state, city, and neighborhood--about harmful chemicals that are released into the environment. Both the cancer and the environmental health files are good examples of the extensive collaboration between the National Library of Medicine and other government agencies in building databases: the National Cancer Institute, the Environmental Protection Agency, Food and Drug Administration, and Centers for Disease Control and Prevention.

I am pleased to tell the Congress that this month we have announced a radically redesigned Grateful Med. This all-new version will provide to users of the Internet and the World Wide Web a way to search MEDLINE with a rapidity and degree of flexibility never before possible. Because the connection is via the NLM's WWW Home Page, the Internet Grateful Med eliminates the need for users to purchase the software and to always upgrade to the latest version on their personal computers. I should note that Internet Grateful Med is the first major accomplishment of NLM under its designation as a "reinvention laboratory." We are embarked on a major effort to overhaul our existing computer-based retrieval system and to take advantage of new directions in software, hardware, and communications.

The Library was an early proponent of health-related uses of the Internet. In fact, NLM had one of the very first Federal agency Home Pages on the World Wide Web. Not only are we making more and more of the Library's publications and database services accessible using the Internet, we have a program to provide funds to help medical institutions connect to the Internet, including small hospitals and free-standing clinics, as well as large medical centers.

Research and Development

One frequent stop by visitors to NLM's Home Page is the section where they may view selected images from the "Visible Human." This is the project that resulted in two computer-generated cadavers, male and female, that are being used by more than 425 educational, scientific, artistic, and commercial licensees in 23 countries. The Visible Human Male, introduced late in 1994, consists of MRI, CT and anatomical images from a single male cadaver. It is about 14 gigabytes in size. The dataset for the Visible Human Female was introduced in November 1995 and has the same basic characteristics as the male, except that the imaging was done to a much finer detail and amounts to some 40 gigabytes. Both male and female have received worldwide press attention. Proposed applications include: multi-media "textbooks" for K to 12 health education and for the teaching of college and medical school anatomy; models for radiation absorption, radiation treatment planning and surgical planning; virtual reality games; professional surgical simulators and endoscopy simulators; and normal reference for teaching clinical diagnosis.

The fast-paced progress in molecular biology and the Human Genome Project is having a great impact on biomedical research and the practice of medicine. The Library's National Center for Biotechnology

Information maintains the most comprehensive collections of genetic sequences in the world and it is a critical resource in the gene discovery process for researchers. NLM's database of DNA sequences, called GenBank, contains 625,000 sequences from 15,000 different organisms and is perhaps the fastest growing of the Library's information offerings. This databank is absolutely crucial for scientists to identify new human genes. The exponential growth in the data has been matched by an exponential growth in public access to it--more than 25,000 searches every day by scientists around the world. In recognition of the Library's central role in genome informatics, representatives of 18 leading pharmaceutical and biotechnology companies met recently at NLM to explore new ways to collaborate with the Library and with each other to develop new computer tools to cope with the rapidly growing body of public genomic data.

There is special excitement about those projects that involve telemedicine. Telemedicine is seen as having great potential for improving the quality of health care, especially where remoteness of patient and provider is a factor. The NLM is funding a number of telemedicine-related projects in such areas as radiology (University of Pittsburgh), neurology (University of California, San Francisco), dermatology (University of Oregon), medical care in the urban setting (Northwestern University), and rural medicine (Iowa and West Virginia). As important as these individual projects are, there is an even greater need to obtain expert guidance on evaluating the potential of telemedicine and its impact on the health care system. To accomplish this, the Library is helping to fund an Institute of Medicine study to develop criteria for evaluating telemedicine, based in part on site visits to actual telemedicine sites. NLM, together with the NIH Clinical Center, is also funding a National Research Council study on how best to ensure the confidentiality of electronic patient records while providing effective access to this information during telemedicine encounters. Criteria developed from these studies will be applied in existing and future telemedicine projects.

The growth of the National Information Infrastructure (NII) and the increasing access to high speed computers and communications by consumers, health care providers, public health professionals, and scientists is having a fundamental impact on health and human services throughout the nation. As part of a multi-agency Federal initiative that fosters the rapid development of high performance computing and communications (HPCC), the Library is investing resources in HPCC medical applications that make use of the National Information Infrastructure. The applications, which all involve the latest information and communications technology, are in such areas as telemedicine, local, state, and regional testbed networks for health care, computer-based patient data, integrating access to health-related information, medical linguistics, and health services research.

Outreach

Recognizing that more health professionals should be using the Library's computer-based information services, the Congress has directed that NLM undertake an outreach program to scientists, health

care providers, and students. There are still far too many health professionals throughout this country who are not aware that NLM and the National Network of Libraries of Medicine exist and work together to provide them with access to the most up-to-date medical information--without regard to where they are located or to the time of day--and to make the information readily and easily obtainable. In response to this challenge, the Library has developed a long-term, wide-reaching effort to make health professionals across the country more aware of the medical information resources that NLM provides, to facilitate their access to these national resources, to train them in the use of Grateful Med, and, whenever possible, to link them to local library services. Close to 300 outreach such projects, involving more than 500 institutions, have taken place since the Congressional initiative began. Although projects have reached out to health professionals of every sort, and in every State, the projects have a special focus on reaching those who have been traditionally "underserved": rural practitioners and those who serve minority populations.

In addition, NLM's outreach is done through exhibits and national, state, and local meetings and through hundreds of training sessions, workshops, and demonstrations. In these endeavors, NLM relies greatly upon the involvement and participation of medical librarians and information specialists at the more than 4,500 institutions that make up the National Network of Libraries of Medicine. Many of the outreach projects aimed at individual health professionals are undertaken by these libraries that serve as NLM's field force. Outreach will not be completed until every health professional in this country knows about the National Library of Medicine and the information resources it makes available.

As we look to the future, we believe that the public will demand ever greater access to health-related information. More and more people are signing onto the Internet; even elementary school students learn how to use it to find information. The Library has already begun a modest shift towards satisfying the needs of the general public, especially in the areas of toxicology and environmental health, HIV/AIDS, and, most recently, clinical practice guidelines for patients that are developed by the Agency for Health Care Policy and Research.

The success of NLM's outreach efforts has increased the demand for its basic library services--acquiring, preserving, and providing access to books, journals, and other materials pertinent to medicine. Libraries throughout the Nation and databases such as MEDLINE and GenBank depend upon NLM's collection and access services. As we continue to develop new health information programs for the National Information Infrastructure we must be mindful that they are founded on traditional library practices. If we fail to keep up with basic services, the result will be a decline in the amount, quality, and timeliness of information services to current health professionals and scholars in the future.

Mr. Chairman, the FY 1997 budget request for the National Library of Medicine is \$143,268,000. I would be happy to answer questions.

DONALD A. B. LINDBERG, M.D.

Donald A.B. Lindberg, M.D., a scientist who has pioneered in applying computer technology to health care, in 1984 was appointed Director of the National Library of Medicine, the worlds largest biomedical library. From 1992-1995 he served in a concurrent position as founding Director of the National Coordination Office for High Performance Computing and Communications (HPCG) in the Office of Science and Technology Policy, Executive Office of the President.

In addition to an eminent career in pathology, Dr. Lindberg has made notable contributions to information and computer activities in medical diagnosis, artificial intelligence, and educational programs. Before his appointment as NLM Director, he was Professor of Information Science and Professor of Pathology at the University of Missouri-Columbia. He has current academic appointments as Clinical Professor of Pathology at the University of Virginia and Adjunct Professor of Pathology at the University of Maryland School of Medicine.

Dr. Lindberg was elected the first President of the American Medical Informatics Association (AMIA) and, since 1992, he has served on the AMIA Board of Directors. As the countrys senior statesman for medicine and computers, he has been called upon to serve on many boards including the Computer Science and Engineering Board of the National Academy of Sciences, the Symposium on Computer Applications in Medical Care (SCAMC), the Organizing Committee for MEDINFO 86, the National Board of Medical Examiners, and the Institute of Medicine Advisory Council of the National Academy of Sciences.

Dr. Lindberg is the author of three books: The Computer and Medical Care; Computers in Life Science Research; and The Growth of Medical Information Systems in the United States, several book chapters, and more than 200 articles and reports. He has served as editor and editorial board member of nine publications including the Journal of the American Medical Association.

Dr. Lindberg graduated *Magna cum Laude* from Amherst College and received his M.D. degree from the College of Physicians and Surgeons, Columbia University. Among the honors he has received are Phi Beta Kappa, Simpson Fellow of Amherst College, Markle Scholar in Academic Medicine, Surgeon Generals Medallion, recipient of the First AMA Nathan Davis Award for outstanding Member of the Executive Branch in Career Public Service, the Walter C. Alvarez Memorial Award of the American Medical Writers Association, the Presidential Senior Executive Rank Award, Founding Fellow of the American Institute of Medical and Biological Engineering, the Outstanding Service Medal of the Uniformed Services University of the Health Sciences, *Federal Computer Week s* Federal 100 Award, Computers in Healthcare Pioneer Award, Association of Minority Health Professions Schools Commendation, the RCI High Performance Computing Industry Recognition Award, and honorary doctorates from Amherst College, the State University of New York at Syracuse and the University of Missouri-Columbia.

March 1996

INTERNET

Mr. PORTER. Doctor Lindberg, will the Internet and the Grateful Med eventually make other access routes to your services obsolete?

Dr. LINDBERG. I think it is by far the preferred route. But I think most interesting, Mr. Porter, is what will Internet become. These things are changing so amazingly fast. Three years ago the World Wide Web was known only to the physics community in Geneva; now it's on everybody's desk, including the members of this distinguished House. So what will it look like five years from now I'm not certain, but I think we can say that it will be multimedia—it will have pictures and colors and movements and sounds. I think we can say that the United States will still be in the lead, and it is in the lead in no small measure because of the strong support for research and development that the Congress has given it. The High Performance Computer and Communications program has been supported by this and the previous administration as well. I think we can safely guess that more and more networks abroad will have joined the Internet. We think that the crossover will be about in 1996, that is to say there will be an equal number, or perhaps more member networks abroad than here.

But I think we can also safely say that there will be places in the United States that won't be as fortunate as we would hope. We know right now that rural areas, inner-city areas, frontier areas simply do not have the ability to attach to the Internet. It is the goal of a number of our programs to enhance that connectivity. We know, for instance, that in 1993 75 percent of all of the university medical centers had Internet connections, but that 60 percent of the non-university affiliated hospitals did not.

[CLERK'S NOTE: Subsequent to the hearing NLM corrected this figure to "75 percent" for the record.]

Dr. LINDBERG. So those patterns we can foresee and yet we don't know the exact final outcome. At the moment, 75 percent of our users can get to Internet, so, therefore, they can use this new Grateful Med. We know that by survey, but we also know that we're going to have to do a little hand-holding to get them to move over and take advantage of what the Internet provides.

HUMAN GENOME

Mr. PORTER. It sounds as if the volume of genome data that will be produced over the next few years will be overwhelming. Do you expect the volume to outstrip the capacity of your data systems to manage it?

Dr. LINDBERG. No, I don't think we are going to be overwhelmed, although it really is hard for us to believe how fast it is growing. For the first few years of the Human Genome Project and the existence of the National Center for Biotechnology Information, the volume of the data taken altogether doubled every 23 months. It is now doubling every 13 months. On the other hand, the technical capability of the high performance computers, largely now cluster machines, I think will probably keep out ahead of it. That's, of course, the technical end of it.

Now, there are two other parts that have to be emphasized. One is the sort of intellectual connectivity. For instance, Dr. David

Lipman who heads the biotechnology center, has arrangements with 15 of the major high volume sequencing centers such that their information comes directly to him, that's to say in a bulk, if you will, an efficient kind of a transfer. But there are many, many thousands of scientists in the United States and abroad who still are contributing individually and of course they need encouragement and training in order to keep that going.

The other part, of course, is the international arrangement. The Human Genome Project is a worldwide project. They exchange really very well with Europe and with Japan. There have been differences of opinion in the United States as to whether these products ought to be patented, held secret until the owner agrees to release them. These are matters that will affect the outcome of this project. But I think technically we will be able to handle the volume. And I think intellectually Dr. Lipman and the other leaders of the Genome Project will be able to make the intellectual connections that will permit really major discoveries to come from the work.

USER FEES

Mr. PORTER. How are user access fees handled on the Internet? Are there developed technologies for charging users to access journals and other documents for which they would normally be billed?

Dr. LINDBERG. I think the answer is definitely yes, but, of course, we're not in the business of charging people to access journals, per se. Obviously, the owners of the copyrights, the publishers are. They are in an interesting position at the moment in which they want to find new ways to work that system. Obviously, a profit-making company has to make a profit.

A number of really interesting experiments are occurring. There is an experiment within the National Center for Biotechnology Information at NLM called Pub Med in which once one has found the publication he or she wants through a MEDLINE search, we can directly link that user, that scientist or—it would usually be a scientist in this case or a clinical physician, to the full text of the article not by our having it in the old way, scanning it in and owning it and charging, but rather linking them through Internet directly to the URL where the publisher has made it available in full text. So this is already happening in the case of some of the major scientific publications, the Journal of Biochemistry, the Journal of the American Medical Association, beginning now with the New England Journal of Medicine. Some of the leading publications are doing this as a kind of an experiment.

In all the cases I have mentioned, there actually is no charge, no dollar charge because they don't know quite how to do it. But in all cases, those publishers have said subsequently some kind of a charge will be rendered, taking into account whether the user is already a subscriber, let's say, to the journal. It will be up to them to make that business decision, but NLM will simply make the connection. We will continue to instantly, literally with the click of a mouse, of a pointing device, connect the user with that URL and make the full-text available instantly.

Mr. PORTER. Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman. Dr. Lindberg, it is nice to see you again.

Dr. LINDBERG. Thank you.

USER FEES

Mr. STOKES. As a user, if I go online into Internet Grateful Med, what would it cost me?

Dr. LINDBERG. Well, actually, it will cost somewhat less than it used to cost you. We've attempted to hold the cost down, although we're under agreement with this committee and the OMB to recover the marginal cost for running the system. What that comes down to in the bottom line is about \$1.00 or \$1.25 per patient oriented search. We also know that many institutions want to simply let's say make a payment for the year and enable all of their faculty and residents to have access under a flat fee arrangement. So we have with 32 institutions that kind of an arrangement. So I have to put you in a category now to give you the right answer, if you're a member of this or that. Then there are eight professional associations who have made a somewhat different arrangement with us. They made an arrangement in which everybody who is a member has the right to pay a fixed dollar amount per year and then have unlimited searching.

So we're struggling to find out what the formula should be. I guess we're looking at the same thing as the commercial publishers, finding what will allow us to satisfy our commitments to this committee and to the OMB and bring in the marginal cost but yet let people have what appears to them essentially to be free and unlimited searching. That's what everybody wants and that's what we're trying to get them.

USE OF NLM SERVICES

Mr. STOKES. Are you in a position to quantify for us what percent of health care professionals use NLM services?

Dr. LINDBERG. That's a good question because obviously we know a great deal about our customers and not so much about our non-customers. I think it has increased over the last 12 years from 5 percent to 20 percent of U.S. physicians who are regular users of NLM's services.

Mr. STOKES. The increase has grown from 5 to about 20 percent.

Dr. LINDBERG. Yes. Now it will be, again, irregular depending on which part of the system that we talk about. And it may be a good bit higher, it may be as high as 25 percent, because we have about 100, 99 actually, agreements to provide MEDLINE and/or other databases to commercial publishers, to universities, CD-ROMs, and to 20 overseas countries. So we're in the business of trying to make it available. Now, when you say CD-ROMs, we have no possible way to measure who uses them and how often, so we're really shooting in the dark there. So my data are probably on the low side, but reliable.

Then again, certain datasets are well used, like MEDLINE; certain others are important but not so well used, toxicology is an example. I am happy to say that with Dr. Mel Spann, who is here with me, we did an experiment there working with nine historically black colleges and universities, HBCUs, with professional schools

because we had done studies to establish that the percentage of their use of the toxicology files was close to zero. We had reason to believe that it should be, if anything, higher than the average because in a sense their population is said to be at more risk for exposure to environmentally dangerous chemicals. So we made a special project in that respect and it is really a big success. If you wish, we could hear more from Mel, but just to hit the highlight of it, we could afford to fund those nine schools, and we, in retrospect, did a good job with it. But he then was able to work with the Agency for Toxic Substances and Disease Registry to co-fund a project such that the spin-off of this, now that we know how to work with those schools, is operating in 52 schools.

[CLERK'S NOTE:—Subquest to the hearing, NLM changed the figure to "59" for the record.]

So, there are areas where we do well and there are areas not so well. We have to study them and we have to correct the areas where we're weak.

OUTREACH

Mr. STOKES. So then, you have some form of an outreach program which reaches these underserved populations?

Dr. LINDBERG. Yes. I was able to say honestly to the committee some time back that I considered that outreach was our absolutely top priority. The committee was good in giving earmarked funds for outreach. Obviously, libraries always do outreach; they don't have books for librarians, they have books for users. But we really didn't have any true outreach program until starting in 1989 when the committee began to earmark funds. It is now at about \$6 million.

[CLERK'S NOTE:—Subsequent to the hearing NLM corrected this dollar amount to \$6.5 million for the record.]

We have concluded nearly 500 projects with 700 institutions. Obviously, I won't start at the top and recite the whole verse to you, but essentially we tried to correct what we thought were deficits: medically underserved populations we know perfectly well are in rural and remote areas, minority populations, and those who serve them, and that's been the case for the last 40 years. So we tried to look at ways in which we could correct the information part of that, if you will, because we have no ability to go and set broken bones and make blood banks. We can do the information part. And that was, one, to get connections; two, to get training of how to use these systems; and then two special areas that we felt warranted focus, namely, AIDS and toxicology. So those are the areas in which we've had specific outreach programs, all carefully measured, all I think pretty successful.

Mr. STOKES. Thank you, Dr. Lindberg. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes. Mr. Miller.

Mr. MILLER. No questions, Mr. Chairman.

TELEMEDICINE

Mr. PORTER. Dr. Lindberg, you have contracted with the Institute of Medicine to evaluate telemedicine's efforts. Was this triggered by specific concerns? And when will the results of the IOM's study be available?

Dr. LINDBERG. Yes, I was concerned myself about the following proposition. I believe, and a lot of our advisors believe, that telemedicine has this very great capability that I expressed to you, but we also have a strong sense of history, because much of the telemedicine experimentation started under regional medical programs thirty years ago, and I've seen it, I've worked in it. And we also know that in those days it was popular, it was enthusiastic, it had support of the Congress and the press and everybody else, then it went away. It was treated almost like a fad.

Now, I think things are a little different. The technology is certainly stronger and better and cheaper. But I think the really critical element in both of those eras is that we have to show medical importance of the work. We have to show medical benefits, we have to show the benefits to whom, and if there are those interested in cost, that's fine, then we want to know if they cost more money or less money and whose money it saved. So with those things in mind—I mean, we could deliver this sort of lecture-like, sermon-like message to grantees but that doesn't do any good, they probably believe it as much as I do. I don't know how to tell them to do that evaluation. Really, it is a difficult scientific problem. I felt that it was best to draw on a scholarly and impartial and capable national resource, namely, the Institute of Medicine, and that's what we've done.

I should say that I understand the amount of humility with which a library ought to approach these kind of problems, and we, I am proud to say, have co-funding of this project from HCFA, Health Care Finance Administration, and from the VA, who are pretty good at it and very much concerned about the delivery of health care. So I have great hopes that a good set of recommendations will come from that study. It will be available this summer.

We're announcing some supplements to the original awards and a solicitation of some new proposals which I hope will be able to look at whatever the IOM recommends and build that into the data collection and test it out so that within a couple of years we'll really have good data evaluating the importance of telemedicine.

REINVENTION LABORATORY

Mr. PORTER. NLM has been designated as a reinvention laboratory which you are using to redesign your computer systems. What additional authority were you granted with this designation and how are you taking advantage of it?

Dr. LINDBERG. There are two elements that were terribly important to us, Mr. Porter, and which we received when we were approved for that experiment. First, we wanted the authority to make surveys. That was very prominent in the whole reinvention concept. We strongly believe in surveying users and in adapting to programs to strengthen our good points and to correct any weaknesses. Secondly, we had asked for essentially "no year" money, to the extent that the funds approved for purchase of computers could be expended when the right time came, because we had seen occasions in the past in which delegated procurement authorities were going to expire and purchases were made prematurely really because of the lapsing of the authority. So we were given the authority to carry those over until the information systems have been

purchased. That's greatly appreciated. The third element had to do with personal service contracts, which we had asked, with the endorsement of NIH, of course, that we be given permission to enter into a personal service contract. Those are very important to us.

VISIBLE HUMAN EMBRYO

Mr. PORTER. We understand there is now a Visible Human Embryo Project underway. Where did the embryos being used come from and what are the main expected uses of the project?

Mr. LINDBERG. I can tell you what I know about it, it's not an NLM project. There is a collection of human embryos called the Carnegie collection which physically resides at the Armed Forces Institute of Pathology and was collected under Carnegie Foundation sponsorship many years ago, many decades ago. They look to me quite important and quite useful. We don't have the resources to do more than we're doing right now. The National Institute of Child Health and Human Development did feel that this was terribly important and that the resource ought not to be wasted or perhaps could never be created again, to be truthful. So they would like to use the techniques that we have described to you in a very general sense for the adult to use for these tiny embryos, the different sizes, so that those who study them would be able to understand better the fascinating embryological changes that occur in their growth. So we're essentially donating technology, understanding; the funding is coming, in my understanding, from National Institute of Child Health and Human Development. The agency that actually has them is the Armed Forces Institute of Pathology and I suspect the American Registry of Pathology is the nonprofit side.

MEDICAL DATA PRIVACY

Mr. PORTER. The problem of maintaining the privacy of medical data when it is made available online in health care facilities seems intractable. What strategies are being considered to preserve patient confidentiality?

Dr. LINDBERG. I think it is a very critical issue, I agree with you completely. There is, of course, before the Congress a bill in both the Senate and the House, I think there's not yet a joint resolution on the matter, and both have been commented on by HHS. We have been asked in turn to give an opinion to the Department. And Senator Kassebaum has had public hearings on the matter in the Senate. I think that the critical element to bring forward is that right at the moment there is essentially no protection for medical records, computerized or otherwise, except a few hit or miss State pieces of legislation, and most States have no such legislation. I think both bills offer in some cases strong criminal penalties for those who violate the terms of the bill and don't preserve the confidentiality of the medical records. Both bills point equally strongly to this necessity whether the records are paper-based or computer-based, and that's an important thing. And both bills make some exceptions, let's say, for the case of medical research.

Amazingly enough, what seems to be a very obvious common good and a strong bill and a noncontroversial bill has run into the sort of whirlwind of multiple opinions that you in the Congress I guess get ultimately used to. I am amazed that there are people

who look at these bills and say they don't correct every possible weakness of the human condition. I think that we need legislation and that this would be an awfully good year to have it.

I could perhaps add one other thing. There are technical matters, there is encryption technology that I could tell you more about than you would want to know. But I think the bottom line is to believe that there's at least enough of it out there to do the job. We need to get some experiments going using encryption technology with real patients, real hospitals, and real doctors to know. It's really a matter of inconvenience, how much inconvenience people will put up with in order to obtain a measure of privacy they desire. It is technically quite easy.

PUBLIC EDUCATION

Mr. PORTER. Do you envision the National Library of Medicine taking over more of the NIH public education effort with its extensive experience in operating online services for the public or will that be the responsibility of the individual institutes?

Dr. LINDBERG. I don't feel able to take over anybody's territory. I think the traditional role of a library is a good way, a good role, and that is that the library specialize and determine to stay ahead on the technical expertise of organizing information, to work in strong partnership with those who have subject matter expertise. Happily, NIH is a remarkably strong place for subject matter expertise in almost every branch of science.

Mr. PORTER. Mr. Miller, any questions?

Mr. MILLER. No questions, Mr. Chairman.

Mr. PORTER. Dr. Lindberg, we are very pleased that the National Library of Medicine has a person of your abilities and understanding as its director, and we thank you for your very fine testimony this afternoon.

Dr. LINDBERG. Thank you, Mr. Porter.

Mr. PORTER. The subcommittee will stand in recess until 10:00 tomorrow.

[The following questions were submitted to be answered for the record:]

GENETIC MAPS

Mr. Porter: Do your data bases contain all the genetic maps that are being produced or do those reside in individual institutions?

Dr. Lindberg: Early gene mapping efforts involved painstaking genetic analysis, but the DNA revolution has led to a profound change in the way gene maps are constructed and used. Following a recent explosion in the amount of available DNA sequence data, several large mapping centers around the world are now placing genes on the map at ever-accelerating rates. However, until recently it has been difficult for others in the biomedical research community to make effective use of this information. This is because it was generally maintained by the individual mapping centers and not available from a central resource. Over the last year we have established working relationships with the largest producers of mapping data, allowing us to collect several different types of maps and integrate them with each other and them with existing sequence and bibliographic records. Even in its infancy, this integrated information resource has already proven useful to a variety of users, including the mapping centers themselves. Our current efforts are aimed at improving the overall ease-of-use of the system and increasing its comprehensiveness.

NLM ACQUISITIONS

Mr. Porter: With so many peer-reviewed journals becoming available electronically, are you changing your estimates for future NLM acquisitions budgets and storage needs?

Dr. Lindberg: While we expect the growth of electronic publishing to have many significant and positive effects on the delivery of biomedical information, we don't expect any decrease in our literature costs. In the short term, as many journals are published in both print and electronic journals, paid subscriptions to the print versions are likely to be required to gain access to the full text of the electronic version. Although most publishers have yet to determine how to collect charges for use of purely electronic publications, it seems likely that they will devise systems that will have costs comparable to current subscription fees. The economics of electronic publishing remain extremely uncertain, however.

The PubMed project is a collaboration between the National Library of Medicine (NLM) and publishers of biomedical journals to link MEDLINE to online journals through the World Wide Web (WWW). Users will be able to search the entire biomedical literature through Medline and link from a Medline abstract to the corresponding full-text version of an article as provided directly from the publisher. PubMed will furnish health-care providers, researchers and students with more rapid and efficient access to the published literature. Because of its role as a public biomedical information provider, NLM is uniquely positioned to create linkages from the publisher's articles not only to MEDLINE abstracts, but also to gene sequences, protein structures, disease descriptions, and clinical practice guidelines. Publishers have shown keen interest in the PubMed concept since it allows them to maintain their own independent

online services while expanding their linkages with other commercial and government health information sources. A variety of major publishers and journals (including Science, New England Journal of Medicine, Annals of Internal Medicine, Journal of Biological Chemistry, Proceedings of the National Academy of Sciences, Oxford University Press, Academic Press, and Blackwell Science Ltd.) are in various stages of evaluation of the PubMed project or are already working on technical aspects of implementation.

The National Center for Biotechnology Information in NLM has already demonstrated the feasibility of this concept by linking a subset of MEDLINE in the area of molecular biology to several online journals. This system, named 'Entrez', is operational and is accessed daily by over 5,000 different sites worldwide.

As far as storage is concerned, electronic publishing will decrease the rate of growth of our collection of printed materials, but we are not sure how rapidly this will occur. Based on recent collection growth estimates, our current on-site space is adequate to store the collection until 2010-14. We are continuing to monitor the situation closely and will do a major reassessment of our space needs in the year 2000. By then we should have a better idea of the rate of conversion to purely electronic publication.

From the perspective of NLM and other large research libraries with archival responsibilities, the most significant and expensive challenge posed by electronic publications may be their long-term preservation. If publishers license access to electronic publications rather than sell copies of them, special negotiations may be needed to allow NLM to obtain copies that can be preserved as part of the scientific record. Given that NLM obtains the right to preserve the material, the preservation of information in electronic form is potentially far more expensive than the preservation of printed material on microfilm. Current electronic media are not as long-lived as microfilm, and, in addition to periodic transfer of the information to new media, resources will be required to ensure that there is current software capable of accessing preserved electronic information. NLM has begun work on a strategy for addressing preservation of electronic publications.

INTEGRATED ACADEMIC INFORMATION MANAGEMENT SYSTEM GRANTS (IAIMS)

Mr. Porter: Have you shifted the focus of your Integrated Academic Information Management System grants from interconnecting multiple sites within a university or medical school to emphasizing connections to the Internet?

Dr. Lindberg: Emphasis on Internet Connection has been added to the IAIMS mission but does not replace it. Our concept is that the information system within a medical center needs to be integrated as an internal network, which then must link to the Internet so as to enable networking of all our medical centers.

Mr. Porter: Is obtaining access to the Internet expensive enough that it justifies NLM assistance grants?

Dr. Lindberg: Making a connection to Internet is not inherently expensive, but CEO's are often reluctant to spend even the relatively small amount of \$30,000 because the value of a connection to a hospital or small medical center is not appreciated. We have found that our grant programs enable organizations to get into the water, after which they quickly become enthusiasts and maintain the connection from their own budgets.

NIH CLINICAL CENTER

Mr. Porter: Are you assisting the NIH clinical center as they upgrade and integrate their patient care and management automated data systems?

Dr. Lindberg: There are a number of ways that NLM will assist the Clinical Center, bringing to bear the combined resources of the two institutions on important health care problems:

- o NLM and the Clinical Center will collaborate on expanding existing NIH databases of clinical research protocols, making all NIH protocols easily available via the World Wide Web.
- o NLM will use its expertise to assist the Clinical Center in interacting with the extramural community (General Clinical Research Centers) in a more interactive way, using telemedicine to engage primary care physicians in clinical research, especially in rural and other isolated sites.
- o NLM will use its expertise to assist the Clinical Center in modernizing its internal information systems, including computer-based patient records and the use of Internet Grateful Med for access to medical knowledge. This will benefit NLM by providing a test bed for its developing new products and services.
- o NLM and the Clinical Center are currently funding the Computer Science and Telecommunications Board, National Research Council, to study current best practices for ensuring confidentiality while providing effective access to electronic health data, during telemedicine encounters, transfer of patient data within health care systems, etc. The Clinical Center will serve as a testbed for experimental application of the guidelines produced by this study.

NLM DATABASE SERVICES

Mr. Porter: What is the current distribution of the users of your data systems -- general public versus health professionals?

Dr. Lindberg: Users access NLM's databases three different ways: through direct online use of the databases on NLM's computer systems; through online use of NLM databases mounted on systems belonging to

the many commercial companies, universities, and other institutions that lease NLM databases; and through commercial CD-ROM products also produced by companies that lease NLM data. As you would expect, we know more about the people who search the databases directly on NLM computer systems than we do about the many thousands who search them on other online systems or on CD-ROM products. Of the roughly 106,000 U.S. users who search the databases on NLM's system, we estimate that more than half are health professionals, and the large majority of these are physicians. NLM also has substantial numbers of users who are scientists, educators, students, and librarians and information specialists. Less than 1 percent of the current direct users of our online databases are consumers or those whose primary focus is the provision of consumer health information. We know that other consumers are searching our databases on CD-ROM products available in public libraries or online through America Online or other database vendors, but we don't know how many. Hospital or public librarians also search our databases on behalf of patients, their families, or the general public, but we don't know how often that occurs either.

No doubt many consumers also use information they find on NLM's Web Pages, without ever applying for a code to search our major databases. We know the total amount of use of our Web site, but we can't identify how much of this is consumer use.

Mr. Porter: How do you expect that to change in the future?

Dr. Lindberg: We expect both the number of health professionals and the number of consumers who search NLM databases to grow substantially. The tremendous growth in consumer access to the Internet coupled with tools like Internet Grateful Med will probably lead to steep growth in the number and percentage of individual consumers who search NLM's databases directly. We should also see steep growth in the number and percentage of public libraries and community organizations that provide ready access to our systems. Although all of our databases offer information of value to persistent and motivated consumers, some of our existing services are particularly useful to the general public, such as the National Cancer Institute's PDQ cancer information database, the practice guidelines sponsored by the Agency for Health Care Policy and Research and other HHS agencies that are available in full-text in HSTAT, the AIDS databases, and a directory database that describes organizations and associations that provide consumer health information on many subjects. We need to do a better job of leading consumers to these resources and to the many excellent consumer health resources produced by NIH Institutes and other government agencies and are currently engaged in collaborative projects to achieve that goal.

HIGH PERFORMANCE COMPUTING AND COMMUNICATIONS

Mr. Porter: Provide the 1995-97 government-wide budget for the high performance computing and communications initiative, separately identifying the budget for each NIH Institute involved.

Dr. Lindberg: The latest data is from the FY 1997 President's Budget Appendix.

Agency	(Dollars in millions)		
	FY 1995	FY 1996	FY 1997
Defense	\$375	\$315	\$337
Health and Human Services	68	81	87
National Institutes of Health (non-add)	(68)	(81)	(87)
National Cancer Institute	7	8	8
National Center for Research Resources	20	22	24
National Library of Medicine	32	42	45
Office of the Director	9	9	9
National Institute of General Medical Sciences	0	0	1
National Aeronautics and Space Administration	131	116	104
Energy	119	121	125
National Science Foundation	297	291	280
Commerce	30	31	34
Environmental Protection Agency	12	12	6
Transportation	24	23	43
Education	16	12	18
Veterans	24	21	16
TOTAL	1,096	1,023	1,050

OUTREACH

Mr. Bonilla: Last year the Committee recommended that NLM report on outreach funding and activities planned for fiscal year 1997 during the FY 97 budget hearing. Dr. Lindberg, are you prepared today to give us a summary of NLM's plans in that area for the coming year?

Dr. Lindberg: Recognizing that more health professionals could benefit from using the Library's computer-based information services, the Congress has directed that NLM undertake an outreach program to scientists, health care providers, and students. There are still far too many health professionals throughout this country who are not aware that NLM and the National Network of Libraries of Medicine exist and work together to provide them with access to the most up-to-date medical information--where and when they need it. The Congress has provided funds for outreach efforts since FY 1990. In response, the Library has developed a long-term, wide-reaching effort to make health professionals across the country more aware of the medical information resources that NLM provides, to facilitate their access to these national resources, to train them in the use of Grateful Med, and, whenever possible, to link them to local library services. Nearly 500 outreach projects, involving more than 700 institutions, have taken place since the outreach program began. Many have had a special focus on reaching those who have been traditionally "underserved"--rural practitioners and those who serve minority populations.

Much of NLM's outreach is done through exhibits at national, state, and local meetings and through hundreds of training sessions, workshops, and demonstrations. In these endeavors, NLM relies greatly upon the involvement and participation of medical librarians and information specialists at the more than 4,500 institutions that make up the National Network of Libraries of Medicine. Many of the outreach projects aimed at individual health professionals are undertaken by these libraries that serve as NLM's field force. Collectively they have trained more than 20,000 individual health professionals across the country to use Grateful Med to obtain up-to-date medical information.

As we look to the future, we believe that the public will demand ever greater access to health-related information. The Library has already begun a modest shift towards satisfying the needs of the general public, especially in the areas of toxicology and environmental health, HIV/AIDS, and, most recently, clinical practice guidelines for patients. In the next fiscal year, we anticipate developing additional new partnerships with public libraries, in an effort to make NLM's resources more widely available to the public through informed intermediaries.

Each day, more and more people are signing onto the Internet; even elementary school students learn how to use it to find information. The Internet has become extremely important in biomedical communication. The NLM has recently announced an "Internet Grateful Med" which permits much faster and more flexible searching of MEDLINE. This Internet version is a radical modification of the extremely popular Grateful Med software that is currently used by most

users of NLM's online network to simplify the process of database searching.

The Internet, in fact, plays an increasingly central role in how the Library makes its information available. NLM's World Wide Web site (called "HyperDOC") is a popular destination for those seeking health-related information. Some 40,000 users a day visit HyperDOC and learn about the Library's many products and services, have access to NLM databases, download the text of NLM reports and publications, and view a variety of visual materials. The NLM supports several ambitious projects to establish testbed networks for health communication, ranging from citywide to statewide to regionwide.

The Internet and the World Wide Web will make possible the fulfillment of a long-felt need to extend the capabilities of MEDLINE beyond references and abstracts so as to permit health professionals to retrieve the full text of scientific articles. The "PubMed" experiment, a collaboration between the National Library of Medicine and publishers of biomedical journals, will link MEDLINE to online journals through the World Wide Web. Users will be able to search the entire biomedical literature through MEDLINE and link from a MEDLINE abstract to the corresponding full-text version of an article as provided directly from the publisher. Because of its role as a public biomedical information provider, NLM is uniquely positioned to create linkages from the publishers' articles not only to MEDLINE abstracts, but also to gene sequences, protein structures, disease descriptions, and clinical practice guidelines. Publishers have enthusiastically endorsed the PubMed concept since it allows them to maintain their own independent online services while expanding their linkages with other publishers and with government health information sources. NLM has already demonstrated the feasibility of this concept by linking a subset of MEDLINE in the area of molecular biology to several online journals.

However, it also is clear that there are several disadvantaged groups which are not readily able to take advantage of the wealth of resources and opportunities that are available through the Internet. From a recent customer survey, we have learned that users in rural locations and at hospitals are less able to sign on to Internet access. In part, this is likely due to lesser availability of means for connections in these locations and, in many cases, to financial constraints. Because the Internet has become so important in biomedical communication, one of the Library's grant programs provides funds to help medical organizations, including small hospitals, free-standing clinics, and managed care organizations, connect to the Internet.

Mr. Bonilla: Currently, does NLM publish an annual report detailing its outreach activities and products which benefit the public?

Dr. Lindberg: NLM publishes several reports which describe its outreach activities, all of which benefit the public through the improved provision of health care services and more timely and widespread reporting of the results of biomedical research. The

official NLM Annual Report is published yearly and contains an update on outreach activities for each fiscal year as well as other NLM programs. Additionally, the Library has recently completed an assessment of the outreach program, entitled Outreach Activities of the National Library of Medicine: A Five Year Review, which assesses the accomplishments of this program in some detail. This report will be published as a supplement to the April 1996 issue of the *Bulletin of the Medical Library Association* which will assure wide distribution of the report to the medical library community and others interested in the program. Outreach accomplishments are also reported on through the NLM News and numerous other publications and reporting mechanisms.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

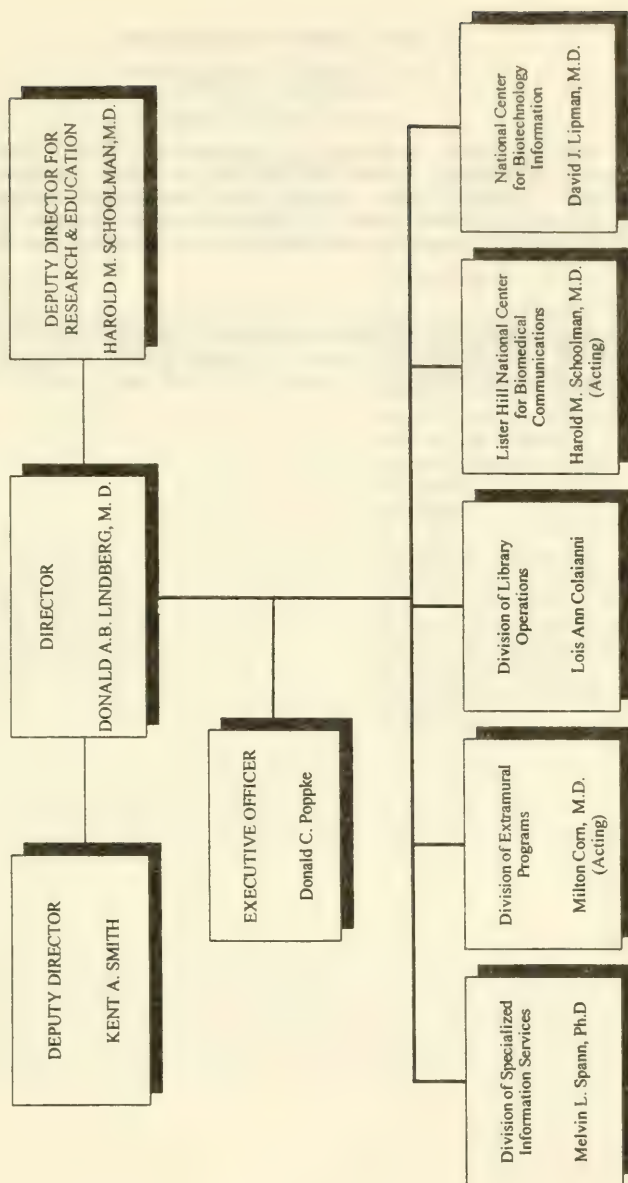
National Library of Medicine

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NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

For carrying out Section 301 and title IV of the Public Health Service Act with respect to the Library, \$143,268,000. Of which \$4,000,000 shall be available until expended for improvement of information systems. Provided, That in fiscal year 1997 and thereafter, the Library may enter into personal services contracts for the provision of services in facilities owned, operated or constructed under the jurisdiction of the National Institutes of Health.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Language Analysis

Language Provision	Explanation
"\$4,000,000 shall be made available until expended for improvement of information systems."	Language has been added to provide NLM needed flexibility in its information system reinvention activities. This will allow procurement actions supporting this multiyear systems development effort to take place without fiscal year constraints.
"the Library may enter into personal services contracts for the provision of services in facilities owned, operated or constructed under the jurisdiction of the National Institutes of Health."	Language has been added to authorize the use of personal services contracts for the information system reinvention activities. This will provide for specialized expertise needed for the duration of the reinvention project.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$126,274,000	\$141,439,000	\$143,268,000
Reduction in accordance with P.L. 103-333.....	-526,000		
Rescission in accordance with PL 104-19.....	-445,000		
Subtotal, Adjusted Appropriation.....	125,303,000	141,439,000	143,268,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-108,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV Activities.....		-3,162,000	
Subtotal, adjusted budget authority.....	125,195,000	138,277,000	143,268,000
Unobligated balance lapsing...	-166,000		
Total, Obligations.....	125,029,000	138,277,000	143,268,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1995--\$12,878,000; FY 1996--\$11,955,000; FY 1997--\$11,955,000.

Also excludes funding for HIV activities: FY 1995--\$2,694,000; FY 1997--\$3,311,000, included in the Office of AIDS Research, NIH.

Justification

National Library of Medicine

1995 Actual		1996 Current Estimate		1997 Current Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
575	\$125,029,000	571	\$138,277,000	571	\$143,268,000	-	+\$4,991,000

General Statement

This document provides justification for the FY 1997 non-AIDS activities of the National Library of Medicine. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Usage of NLM databases continues to rise steadily in terms of individuals connected to the online network and the number of searches they do. Some 30,000 user codes were added to NLM's online network in 1995, bringing the total to more than 130,000 users. This is a 30 percent increase in one year. These users conducted 7.5 million searches, primarily on MEDLINE, NLM's largest database. This continued growth reflects the continuing need of the health professions for access to the latest published knowledge. We estimate that approximately half of the searches are for purposes of patient care and are conducted in hospitals, clinics, and the offices of individual health professionals around the country. The remainder of the searches are conducted for a wide variety of purposes, including medical research, education, and for informational purposes by patients and the general public.

The actual count of how often MEDLINE was consulted, however, is unknown and unknowable. There are 20 formal arrangements between NLM and major government institutions in other countries to provide MEDLINE access around the world. We do not have an accurate count of the number of services they provide. Similarly, we do not know how many millions of online searches are done by users of commercially produced MEDLINE CD-ROM products and by users of large online vendors who mount NLM's databases on their own computers and provide online access. In summary, however, it may be said that NLM's MEDLINE is by far the most-consulted medical information database in the world and that it is available to health professionals in all countries of the world.

More Users, More Capability

MEDLINE contains 8.4 million references and abstracts from the worldwide biomedical literature from 1966 to the present, taken from 4,000 journals published in 40 languages. In 1995, 392,000 references were added to MEDLINE. Other databases contain bibliographic records on AIDS, cancer, bioethics, and environmental health, for example. In addition to references and abstracts to journal articles there are large bibliographic databases related to audiovisuals and monographs in the health sciences. There are other NLM databases containing

hazardous substance information that may be used in emergency situations at the site of a chemical spill. A different kind of database made available over NLM's network contains the full text of Clinical Alerts announced by components of the National Institutes of Health.

A new database, SPACELINE, joined MEDLINE and the others in NLM's family of databases in 1995. SPACELINE is a joint venture with the National Aeronautics and Space Administration and contains some 100,000 records for journal article references (and abstracts), technical reports, books, book chapters, conference proceedings, and audiovisual materials about life science research related to space. Another new database is HSRProj. This database allows access to descriptions of projects in health services research being supported by grants and contracts from Federal and private sources, including NIH institutes, the Agency for Health Care Policy and Research, the Department of Veterans Affairs, and foundations such as the Robert Wood Johnson Foundation. HSRProj joins a growing set of NLM databases dealing with various aspects of health services research, including cost, access, quality, and technology assessment.

The Library is announcing the appearance of a radically different version of the extremely popular Grateful Med software. Grateful Med is used by most users of NLM's online network to simplify the process of database searching. The Internet Grateful Med, as the new system is called, incorporates many new features to help users improve their searches, including the ability to call on the Unified Medical Language System for help. This new software is a key component of the Library's system reinvention initiative that is aimed at replacing NLM's current mainframe computer system. Because the Internet Grateful Med requires users to access NLM via the Internet, it has the potential for greatly expanding foreign usage. The Internet, in fact, has become so important in biomedical communication that the NLM provides small amounts of money to help medical organizations connect to the Internet. A wide variety of organizations has been funded over the last several years, including small hospitals, free-standing clinics, and large medical centers.

Hyperspace and High Performance Computing

The Library's World Wide Web site (called HyperDOC) continues to be a popular destination for those seeking health-related information. Some 40,000 users a day visit HyperDOC and learn about the Library's many products and services, have access to NLM databases, download the text of publications such as NLM newsletters and fact sheets, and view a variety of visual materials. In this last category, NLM's Images from the History of Medicine service allows HyperDOC users to search through 60,000 pictures from the NLM collection and to view selected images.

One frequent stop by WWW visitors is the section of HyperDOC that has selected images from the "Visible Human." This is the project that resulted in two computer-generated cadavers, male and female, for use in a variety of educational, scientific, artistic, and commercial ways. The male (15 gigabytes in size), which was announced in 1994, is now being used by almost 400 licensees in a variety of ways: virtual colonoscopy simulator, modeling radiation absorption, medical school anatomy curricula, and design of ergonomic furniture are just a few examples.

The dataset for the Visible Woman, introduced in November 1995, is 40 gigabytes in size and thus may be viewed in significantly higher resolution than the male. The images for both 3-dimensional cadavers are derived from state-of-the-art radiographic and photographic techniques carried out by scientists at the University of Colorado under contract to the Library.

Progress is being made under the dozen High Performance Computing and Communications health care applications contract awards made by NLM. Although these 3-year projects still have more than a year to run, encouraging results were reported at a meeting of the principal investigators in 1995. The projects were reported in three groups: imaging (for example, teleradiology, teleneuroimaging); networks (such as a citywide patient care network, a statewide testbed network, and a rural patient care network); and an "other" group that included a system built around a new metropolitan medical facility and a project involving organ modeling support for virtual surgery simulation. Near the top of the list of common concerns was how to maintain privacy of medical data and how to evaluate the health care benefits versus the costs of the projects. These two subjects are so crucial, in fact, that the National Library of Medicine has asked the Institute of Medicine to convene panels to study both privacy and evaluation issues related to telemedicine. NLM plans to supplement several of the telemedicine-related projects in 1996 and, if possible, to make new awards in this crucial area.

Outreach

The Library continues to make special efforts to increase usage of its online databases and other information services. The goal of all this outreach activity is to let American health professionals know that modern computer-based information services can be of inestimable help in their work, and that no matter where they live or practice they have convenient and inexpensive (sometimes free) access to NLM's immense data resources. A key to all of NLM's outreach efforts is the cooperation of the eight Regional Medical Libraries and the 4,100 member institutions of the National Network of Libraries of Medicine. Some 50 major exhibits and hundreds of training sessions, workshops, and demonstrations, are conducted annually under the auspices of the Regional Medical Libraries. A planning panel report published by NLM in 1995, *The Education and Training of Health Sciences Librarians*, was widely distributed throughout the profession. It makes a variety of recommendations on how the NLM and other institutions can assure an adequate number of health sciences librarians properly educated and trained to take advantage of the new communications technologies.

Streamlining and Reinvention

The NLM, like all Federal agencies, is affected by the National Performance Review and the President's initiative to reduce the size of the government while maintaining the quality of service it provides. Over the next several years the Library must reduce its staff, increase the ratio of employees to supervisors (to 12 to 1), reduce the number of certain targeted positions, and modernize its information systems. All NLM employees have been invited to participate and to suggest ways to improve. In addition to downsizing the Federal workforce, the National Performance Review identified a set of recommendations to improve services to the public. Federal agencies were asked to establish what they called "reinvention labs" to function as test

sites for agency streamlining and deregulation. The NLM was identified as such a test site and it is now involved in a major initiative to redesign existing computer systems to take advantage of new directions in software, hardware, and communications.

Research and Development

The NLM director, who had served concurrently as director of the High Performance Computing and Communications National Coordination Office since September 1992, stepped down from that position early in 1995. The HPCC, which organizationally is part of the White House Office of Science and Technology Policy, is the multi-agency Federal initiative that fosters the rapid development of high performance computers and networks and the use of these resources throughout the nation. Because of its close association with the Library and the NIH over the past several years, HPCC now includes medicine as an important component.

The Library is investing resources into HPCC medical applications—including projects with heavy information and communications involvement, such as telemedicine, medical imaging, electronic patient records, expert systems, medical linguistics, and testbed networks. These projects are being coordinated by NLM's research and development component, the Lister Hill National Center for Biomedical Communications. Another area of science that is tied intimately with HPCC is that of biotechnology. The National Center for Biotechnology Information, a research component of the NLM and an important component of the national Human Genome Program, creates and maintains systems for storing, analyzing, and retrieving information on molecular biology, biochemistry and genetics. The GenBank database is doubling every year both in size (it now contains 620,000 sequences) and in use—there are now more than 25,000 GenBank queries every day from scientists around the world. The Center has also taken the lead in creating a new experimental system that will enable users to search the biomedical literature through MEDLINE and link from MEDLINE records to the corresponding full-text Internet version of recent articles as provided directly by publishers over the World Wide Web.

The President's appropriation request of \$136,311,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Library of Medicine during the last five years has been as follows:

<u>Year</u>	<u>Amount</u>	<u>FTE's</u>
FY 1992	\$98,031,000	638
FY 1993	102,512,000	625
FY 1994	115,237,000	597
FY 1995	125,029,000	575
FY 1996	138,277,000	571

Purpose and Method of Operation

To maintain information services in support of research, health care delivery, and education, the Library's programs are conducted and supported through the following activities: extramural programs, intramural programs, and research management and support. The primary goal of these activities is to ensure maximum application of biomedical knowledge and state-of-the-art health care improvements resulting from advances in biomedical research.

Overall Budget Policy

The FY 1997 budget request for the National Library of Medicine is \$143,268,000, an increase of \$4,991,000 over the comparable FY 1996 level of \$138,277,000. The request includes support for 571 FTEs, the same level as FY 1996. The request continues to emphasize support for library operations including literature acquisition, management, dissemination, and preservation, and for grants in Integrated Advanced Information Management Systems, training, medical informatics, biotechnology and other research and development activities. The request includes a program increase of \$9,966,000 for High Performance Computing and Communications. This level will permit NLM to institute new programs and enhance existing programs in connectivity, visualization, and database technology that may have profound impact on medical practice, research, and education. For extramural programs, the FY 1997 request is \$33,783,000; an increase of \$498,000 over the FY 1996 comparable level of \$33,285,000. The request will support a total of 164 awards. For intramural programs, the FY 1997 request is \$101,923,000; an increase of \$4,493,000 over the FY 1996 comparable level of \$97,430,000. For research management and support activities, the FY 1997 request is \$7,562,000; the same level as FY 1996.

National Library of Medicine

Extramural Activities

1997 Authorizing Legislation - Section 301, 465-467, and 469-477 of the Public Health Service Act. 1997 Authorization: Indefinite.

Budget Authority:

FY 1995 <u>Actual</u>	FY 1996 <u>Estimate</u>	FY 1997 <u>Estimate</u>	Increase or <u>Decrease</u>
\$30,783,000	\$33,285,000	\$33,783,000	+\$498,000

The NLM's Extramural Programs (EP) Division provides a range of grants relating to the management, dissemination, and use of medical knowledge. Authorized by Public Health Service laws including the Medical Library Assistance Act (MLAA), these grants provide support for research, development, and resources relevant to informatics and biomedical information management in general. In recent years the grant program has concentrated heavily on research and development issues designed to expand the ability of computers and telecommunications to support research, clinical practice, and administration in the health field. NLM administers the major Federal program concerned with biomedical informatics.

Funding for the NLM Extramural Programs during the last five years has been as follows:

FY 1992	26,741,000
FY 1993	26,552,000
FY 1994	28,419,000
FY 1995	30,783,000
FY 1996	33,285,000

Rationale for Budget Request

The FY 1997 budget request for NLM's Extramural Programs is \$33,783,000 which will support approximately 164 awards. This represents an increase of \$498,000 and an increase of 19 awards over the FY 1996 estimate of \$33,285,000. The FY 1997 extramural request will provide support for the following activities: Medical Library Assistance, \$17,558,000, an increase of \$452,000 or 2.6 percent over the FY 1996 estimate of \$17,106,000; PHS 301, \$16,225,000, an increase of \$46,000 or .28 percent over the FY 1996 estimate of \$16,179,000.

Medical Library Assistance Programs

Integrated Academic Information Management System (IAIMS) Program—The IAIMS initiative is designed to provide a comprehensive computerized information system for service to health professionals in complex academic health centers. IAIMS fosters integration of the numerous disparate information subsystems within an organization so as to provide the appropriately authorized user with rapid access to various institutional databases, including

patient records, laboratory tests, previous treatment protocols, pertinent bibliographic databases, remote files--such as a tumor registry in another state--administrative data, and clinical decision-making systems. The program now requires the recipient institution to work toward networking and linkage with the National Information Infrastructure.

To meet changing national needs, IAIMS was significantly revised in 1992 so as to shorten the development time, and to place greater emphasis on clinical elements such as quality control and outcome analysis, and on connections to national information networks. NLM plans to add two new operational grants by end of FY 1997.

Medical Library Resource Grants--Resource Grants assist health science libraries to improve information services to health personnel engaged in education, research and patient care. Present emphasis for the resource grants is on facilitating connection to national databases by networks for both health professionals and librarians. As the new technology penetrates the workplace, biomedical information will more and more be retrieved from a vast national library, composed of a myriad of local collections which are available to all through computers and telecommunications. This program offers two types of grants: Information Access Grants and Information Systems Grants.

The Information Access Grant is directed towards the libraries of small and medium-size hospitals and similar health-related institutions, and promotes access to information resources via new technologies. The Information Systems Grant, which also emphasizes computer and telecommunications technologies, is directed towards larger hospitals and academic health centers, and encourages networking, connectivity and systems integration. This program will be continued and expanded in 1997 due to the marked increase in applications now being received.

Research Grants in Medical Librarianship and Medical Information Science--NLM offers assistance for research and career development opportunities in Health Science Librarianship and Information Science. Investigations in this program area include evaluation of managerial and organization structure for improved information service, studies of how health information professionals perceive their information requirements, and how medical institutions can utilize new technologies to facilitate access to information access. The program is expected to receive increased emphasis in FY 1997 because of the rapidly expanding awareness among health professionals of the utility of the Internet.

Training in Medical Informatics and Biotechnology Information--NLM is the prime supporter, nationally, of university programs which provide research training in medical informatics, and the related subfield which deals with biotechnology and molecular biology. Such programs are designed to train investigators who are well-equipped to address fundamental issues in the management of health knowledge. Trainees in this program will contribute to the growth of information sciences by analyzing special structures for managing this knowledge and will enable biomedicine to take advantage of the enormous capabilities of computer science for organizing, retrieving, and utilizing health knowledge.

To complement research training, NLM also funds a fellowship in applied informatics which is intended to fill an urgent national need for informatics professionals able to bring the results of research into practice. The fellowship will provide up to three years of training for those interested in learning some aspect of informatics which can then be applied to their primary discipline. IAIMS, newer library methods, computerized patient records, informatics aspects of radiotherapy, dentistry, and nursing, artificial intelligence programs, and medical education are among the areas which may be studied by such fellows.

The institutional training program reached its steady state in FY 1995 with about 120 fellows enrolled nationally. The fellowship in applied informatics has been particularly popular and will be significantly increased in FY 1996 because of the importance of such trained personnel in developing the new electronic information systems within our health institutions.

Because the five year grant period for the institutional programs expires in June 1997, NLM will reissue a request for applications for these grants in FY 1996.

EP's Internet Connections Program and the High Performance Computing and Communications (HPCC)--In consonance with the HPCC initiative, Extramural Programs plans to repeat the now annual program first offered in 1992 which provides funds to connect medical institutions to the Internet. A broad variety of health-related institutions including small community hospitals, are eligible to apply. The Internet, like the telephone system, will require a critical mass of users if it is to serve the biomedical community properly.

Outreach Initiative--NLM continues to extend its outreach program to improve access by health professionals to NLM's information products and services and to health-related information sources produced by other Federal agencies. In FY 1997, NLM will fund the second year of the five year contracts for Regional Medical Libraries in eight geographic regions to support the outreach and service programs of the National Network of Libraries of Medicine. The NN/LM focus will be on bringing authoritative, current information to health professionals in all parts of the country, with special outreach programs to rural and minority health professionals, as well as those not affiliated with institutions that provide information services and on linking health professionals to the Internet and therefore to the global biomedical community. NLM will also continue to fund special outreach efforts to community-based AIDS organizations, to producers and users of health services research, and to public health professionals.

In training, the newly established Fellowships in Applied Informatics have as one goal the training of professionals from underserved areas who can then return to their home institutions with the expertise needed to develop and implement modern biomedical information systems.

Almost all of the Information Access grants, and many of the Information Systems grants involve rural or inner city institutions. For FY 1997 NLM expects to continue an increased emphasis on inner cities, which have so far received less support than rural areas.

Publications--The Publication program is small but vital because few alternate sources of support are available. This program provides small grants to scholars, primarily in the field of history of medicine and science, who seek partial support while preparing a manuscript for publication. In FY 1997 EP expects to continue an expanded definition of publication so as to include electronic media.

PHS 301 Programs

Medical Informatics Research--Through the medical informatics program, NLM supports work on fundamental knowledge issues. These concern the extraction, organization, retrieval, and utilization of knowledge, involving methodologies such as artificial intelligence, computer sciences, computational linguistics, medical decision sciences, cognitive psychology, and related information-oriented fields. Funds in FY 1997 will permit funding of six to ten new grants in this area. NLM expects to see particular emphasis on telemedicine, artificial intelligence programs to assist retrieval of stored information, and expert systems to assist medical decision making.

Biotechnology Information Research--In the area of biotechnology information, extramural research is supported to investigate effective methodologies of reorganizing and analyzing data relating to molecular control of life processes. Relevant problems include designing and managing databases, retrieving information from multiple factual databases, and pattern-matching algorithms for biological sequences. Scientific advances in molecular biology will depend in large part on successful resolution of knowledge and information issues. Grants in this area will increase. In addition, NLM expects to focus more support on vital national databases in protein structure and function which can serve as a national resource for investigators in this field. For FY 1997 NLM will continue to place emphasis on protein databases, genome sequence databases, and image databases which capture the physical structure of genetically-relevant molecules. The growing problem of providing support for the rapidly proliferating databases which now underlie much of clinical practice and biomedical research is currently being evaluated.

Computerized medical records--With support from HPCC funds, NLM, in cooperation with the Agency for Health Care Policy and Research, is supporting an important Cooperative agreement granting program in the general area of the Electronic Medical Record System. NLM agrees with the widely-held belief that a nation-wide digital information base for documenting patient care is essential to modern health care management. A practical computerized patient record system must be developed if a national clinical database is to be achieved. The eight awards which have been made in this program have permitted creation of an interacting group which holds great promise for facilitating development of such key elements as a national machine-readable health sciences vocabulary, standards for interchange of information, and safeguards for privacy of clinical information. Because of the central importance of electronic health records, this grant program has a high priority in FY 1997.

Educational Technology--the potential of computers and telecommunications for health education both for professionals and consumers is enormous but much remains to be done in the area of research and development. NLM has supported such work from time to time in its other programs and intends in FY 1997 to set aside some funds dedicated to this important area.

The NLM's Extramural Programs (EP) Division provides a range of grants relating to the management, dissemination, and use of medical knowledge. Authorized by Public Health Service laws including the Medical Library Assistance Act (MLAA), these grants seek to improve biomedical communication and knowledge access and represent the only Federal programs focusing on information issues that concern the entire health community.

National Library of Medicine

Intramural Activities

1997 Authorizing Legislation - Section 301, 465-467, and 478 of the Public Health Service Act.
1997 Authorization: Indefinite.

Budget Authority:

1995		FY 1996		FY 1997		Increase or Decrease	
<u>Actual</u>		<u>Appropriation</u>		<u>Estimate</u>			
<u>FTE</u>	<u>BA</u>	<u>FTE</u>	<u>BA</u>	<u>FTE</u>	<u>BA</u>	<u>FTE</u>	<u>BA</u>
477	\$86,147,000	473	\$97,430,000	474	\$101,923,000	+1	+\$4,493,000

NLM's intramural activities are carried out by four major components: Library Operations acquires and preserves library materials pertinent to medicine; organizes these materials by cataloging and indexing; disseminates its authoritative bibliographic records online, in other machine-readable formats, and in publications; lends originals or copies of documents from NLM's comprehensive collection; provides reference and research assistance as a back-up to services available from the National Network of Libraries of Medicine; and develops and enhances information services in the field of health services research.

The Lister Hill National Center for Biomedical Communications explores the use of computer, communication, and audiovisual technologies for improving the organization, dissemination, and utilization of biomedical information. The National Center for Biotechnology Information performs basic and applied research using mathematical and computational approaches; collects and organizes molecular sequences data; develops software tools for analyzing and accessing data; and distributes data through high-speed network-based systems and other electronic media.

The Specialized Information Services (SIS) manages the Toxicology Information Program (TIP) and develops computerized databases in pharmacology, toxicology, and environmental sciences. They include data related to long-term, low-level exposure to hazardous substances, and on the health effects induced by chemical carcinogenesis, teratogenesis, and mutagenesis. TIP is one of the Nation's most important sources of information for emergency response to toxic chemical spills and the release of other health and environmental or occupational hazards.

Funding for the Intramural Programs during the last five years has been as follows:

<u>Year</u>	<u>Amount</u>	<u>FTE's</u>
FY 1992	\$63,326,000	531
FY 1993	67,865,000	521
FY 1994	78,828,000	495
FY 1995	86,147,000	477
FY 1996	97,430,000	473

Rationale for the Budget Request

The FY 1997 budget request for Intramural Programs is \$101,923,000. This is an increase of \$4,493,000 over the FY 1996 comparable level of \$97,430,000 and will provide increased funding for the high performance computing and communications initiative.

Library Operations

NLM's basic mission is to collect, organize, and provide access to information in the world's biomedical literature in support of the progress of medicine and the improvement of public health. Library Operations acquires and preserves the biomedical literature; organizes this literature through authoritative cataloging and indexing, using the biomedical subject thesaurus it develops and maintains; disseminates NLM bibliographic records online, in machine-readable formats, and in publications; lends or copies documents in the NLM collection as a back-up to document delivery service provided by other U.S. biomedical libraries; provides reference and research assistance to health professionals; and maintains an active program of scholarship in the history of medicine. Library Operations also directs the National Network of Libraries of Medicine (NN/LM) to enhance the general level of biomedical information service available to health professionals throughout the United States. In FY 1997, NLM's System Reinvention will continue to move automated support for many of these essential programs and services to a new and more powerful technical platform. A streamlined approach to responding to many customer inquiries will help the Library to handle steadily increasing user demand for services.

Acquisition--NLM is the largest biomedical library in the world, with a collection of 5.1 million items including books, journal volumes, theses, pamphlets, audiovisuals, computer software, microforms, pictures, and manuscripts. To maintain and enhance this comprehensive collection, in FY 1997 the Library will continue to purchase the world's biomedical literature in a variety of formats. Although electronic publishing is increasing, no corresponding decrease in printed publications is likely to occur in FY 1997. The cost of biomedical literature will continue to increase at a rate that far exceeds inflation. About 65% of the literature acquired by NLM is published outside the U.S. and is sensitive to fluctuations in currency exchange rates. By FY 1997, use of a commercial integrated library system should be supporting more efficient handling of library materials from order to receipt to subsequent use.

Collection Preservation and Maintenance--NLM works to ensure the long-term availability of the scholarly record of biomedicine by preserving endangered items in its collection and promoting the use of more permanent materials in new biomedical publications. In FY 1997, the Library will use contract assistance to bind about 25,000 volumes, microfilm 3,000-5,000 brittle books and journal volumes, and conserve 100-200 rare or unique items from its rare book, manuscript, picture, and audiovisual collections.

Creation of Bibliographic Data--One of NLM's most important activities is the creation of the authoritative records that describe available biomedical information sources, including journal articles, books, and electronic databases. These records provide an essential foundation for the Library's online retrieval, reference, and document delivery services. In FY 1997, NLM expects to describe the contents of 380,000-400,000 articles, 22,000 books, and hundreds of electronic biomedical information sources available on the Internet. The Library will obtain assistance for this work from contracts, interagency agreements, International MEDLARS Centers, and producers of electronic information sources. The NLM System Reinvention will provide more rational and integrated automated support for data creation. Increasingly, NLM will use electronic publication data supplied by publishers to streamline production of its authoritative indexing records and will provide links between its indexing records and available electronic full-text of documents. Library Operations and NLM's Lister Hill Center will be exploring ways to reduce the level of human effort required to produce indexing records without compromising retrieval effectiveness.

Dissemination of Bibliographic Data--NLM's authoritative bibliographic data are distributed online, in various machine-readable formats, and in a diminishing set of printed publications. In FY 1997, NLM will continue to emphasize electronic dissemination of its data via the Internet and will phase out printed publications that have been superseded by more effective electronic resources.

NLM has more than 120,000 online users and expects this number to continue to increase at least 15 percent per year, due to outreach efforts, convenient pricing arrangements, expanded public access to the Internet, increases in the amount of useful electronic information available from the Library, improved retrieval software and Grateful Med interfaces implemented as part of System Reinvention, and enhanced ability to interact with external systems, including patient data systems. In FY 1997, NLM will make more sophisticated use of its UMLS Knowledge Sources to assist users in identifying databases with relevant information and constructing successful searches. Consolidation will have reduced the number of different databases, providing easier access for users and reducing database production and maintenance overhead. NLM will continue to collaborate with a wide range of federal agencies, including other NIH components, the Agency for Health Care Policy and Research, the Centers for Disease Control and Prevention, and the National Aeronautic and Space Administration, to provide cost-effective access to a broad range of health-related information.

Reference Services and Document Delivery--NLM provides reference service and document delivery as national back-up to services available from the more than 4,600 members of the National Network of Libraries of Medicine, as well as serving onsite users of NLM's collection. By FY 1997, NLM will have reorganized its approach to handling reference questions from offsite users and other types of customer service inquiries now handled throughout the Library to provide more rapid and efficient service. The Library expects to respond to more than 300,000 customer service inquiries and to process more than 600,000 document requests in FY 1997. By that time the number of health sciences libraries using DOCLINE, NLM's automated request and routing system, is likely to be about 3,000 and the system is likely to be handling an annual volume of more than 3 million document requests, including many automatically referred by individual health professionals who use the Loansome Doc feature of Grateful Med. Both DOCLINE and NLM's online retrieval system will alert users when the documents requested or identified are available in electronic form via the Internet and will support easy connections to the electronic versions. Of the many requested documents that will not be permanently stored in electronic form on the Internet, an increasing percentage will be scanned as requested and transmitted via the Internet. NLM will continue to work through its National Network of Libraries of Medicine program to increase the number of health professionals with high speed connections to the Internet that allow the most efficient use of many of the Library's services.

Health Services Research--NLM's National Information Center on Health Services Research and Health Care Technology coordinates library-wide efforts to improve access to information needed by health services researchers and to disseminate the results of health services research, including clinical practice guidelines and technology assessments, to health care professionals, administrators, policy makers, and public health officials. In FY 1997, the Library will continue to index health services research literature, including technical reports and government publications, and to enhance or build databases of full-text clinical guidelines, health services research-in-progress, and tested survey instruments. In collaboration with the National Network of Libraries of Medicine and other DHHS agencies, NLM will continue to focus special outreach efforts on public health officials and to train the country's health sciences librarians to respond to health services research information needs and to contribute to local health services research projects.

Better computer-based patient record systems will allow extensive health services research data to be produced as a by-product of current health care. In FY 1997, NLM and the Agency for Health Care Policy and Research will analyze the results of a large-scale test of the extent to which existing vocabularies integrated in the UMLS Metathesaurus can meet the need for standard terminology for patient records and public health information systems. The test should help to determine the resources required to complete and maintain a U.S. standard vocabulary and to identify the appropriate role for the federal government in the maintenance of such a standard.

Lister Hill National Center for Biomedical Communications

Biomedical information exists in text, data, sounds, pictures and many other forms. Developments in computer technology and networks can provide the foundation for new accuracy and speed in organizing, storing, and retrieving each of these forms of biomedical information. The right combination of computer, system, network, and software can put clinical information within the reach of the physician in the office, classroom, hospital, or laboratory when it is needed most.

The Lister Hill National Center for Biomedical Communications has assisted the NLM for over 25 years as its primary research arm in applying technology to improved information delivery and support to the health community. This research which is conducted in the emerging field of medical informatics has enabled the NLM to provide better and more complex service both directly and through the supported network of medical libraries (NNLM). It has increased the tools available to a biomedical user community which is becoming increasingly competent and which demands more precision in the services to which it has access.

Research conducted and supported by the Center included areas of computer technology as varied as the display and analysis of three dimensional electronic images of human anatomy for more accurate instruction of health professions students, to the development of software to move and display radiographs and literature containing critical clinical information. The Center's research also includes the development of natural language understanding programs to enable computers to "read" and "understand" users' questions. In FY 1997 LHCBC will focus its staff and resources on several major program efforts:

Three Dimensional Anatomic Imaging. The Center continues work on its "Visible Human Project™" to construct a digital library representing complete human anatomy at sub-millimeter level resolution. The long term goal of the project is to produce a system allowing one to search for images using words and concepts. Currently LHCBC is distributing the Visible Human data set on digital tape, and over the Internet; and constructing an image database system. In fiscal year 1997, the Center will extend the image data distribution and alpha test the database of three dimensional images.

In FY 1996, The Lister Hill Center has begun a major project to investigate automated methods for indexing and classifying the biomedical literature. NLM is well-known for its high quality indexing of this literature, yet the current practice of manual indexing of journal articles and other biomedical documents is highly labor intensive and expensive. The Next Generation Indexing project will use the expertise of research staff in artificial intelligence especially in the fields of expert systems, natural language understanding, and cognitive science. The center will explore ways to use high performance computing systems to increase the accuracy and automation of identifying and classifying the many forms of information to which health professionals seek access. Such strategies will try to maintain or even improve retrieval of important information; hopefully at the same time reducing the degree of human input.

Telemedicine Collaborative Research. In FY 1996 the LHCNCB continued supporting collaborative research in biomedical applications of computing and digital communications.

The 12 projects, scattered across the nation, fund health care applications such as testbed networks to share information resources, computerized patient records, and medical images; Telemedicine projects to provide consultation and medical care to patients in rural areas; and advanced computer simulations of human anatomy for training via "virtual surgery." Two areas of common concern of the principal investigators of these projects are how to maintain privacy of medical data and how to evaluate the health care benefits versus the costs of the projects. NLM plans to supplement several of the telemedicine-related projects in 1996 and, if possible to make new awards in this crucial area. These projects will continue to be supported in Fiscal Year 1997. The published results and applications demonstrated will guide health care community efforts in the continuing expansion of Telemedicine as efforts to increase efficiency in health care delivery require more extensive use of computer and communications technologies. After completion of these contracts, additional research will be funded through new contracts, grants or cooperative agreements..

In FY 1996, Lister Hill Center staff began a new project in Telemedicine to identify barriers to the use of technology in improving access to health care. This project will identify goals for both collaborative and intramural technology research. Lister Hill engineering and computer scientist staff will also continue to investigate methods for real time access to patient data, records, literature, and laboratory results. The Center sponsored an Institute of Medicine project to define criteria which could be used to properly evaluate the need for or use of telemedicine in particular situations.

Unified Medical Language System. NLM's UMLS Project develops, tests, and implements Knowledge Sources and software that help health professionals and researchers to overcome the barriers to effective information retrieval caused by the differences in the vocabularies used in different types of information sources and by the huge number of separate databases and systems that may have information relevant to a particular question. The 1997 editions of the UMLS Knowledge Sources and associated programs, available to systems developers and other users via the Internet, will have substantial additional content and functionality useful in building computer-based patient records, in UMLS products such as NLM's Internet Grateful Med which assist health professionals to formulate more effective queries and access better and more complete information, and in connecting patient records to relevant sources of electronic information at NLM and elsewhere. Improvements to the UMLS Information Sources Map will support automated selection of the databases most likely to contain information relevant to particular questions.

National Center for Biotechnology Information

The National Center for Biotechnology Information (NCBI) is responsible for managing and distributing the rapidly mounting body of information in the field of molecular biology, particularly genetic sequence information. The identification of new human genes, for example, breast cancer and early-onset Alzheimer's disease, is advancing at an unprecedented pace. These

discoveries are based on DNA sequence information and depend on finding related genes from other organisms in order to understand the underlying biochemistry and physiology of the newly discovered genes. NCBI's mission is to support researchers in industry and academia in gene discovery by maintaining the most comprehensive collection of DNA sequence information in the world, by providing high-performance search systems for these databases on the Internet, and by developing new analytical techniques for genomic data.

NCBI maintains one of the most comprehensive archives of sequence data in the world, GenBank, a collection of nearly half a million DNA sequences from 15,000 different organisms. The database has seen an explosive growth over the past year largely due to a collaboration with Merck and Company, and Washington University whereby over 200,000 human gene sequences (out of an ultimate set of 300,000 sequences) are now available to medical researchers without restriction. NCBI has developed the computing infrastructure to facilitate researchers' access to DNA sequence information through the Internet. The exponential growth in the data has been matched by an exponential growth in public access to it – over 25,000 searches of Gen Bank daily by over 100,000 different sites in the past year.

In FY 1997, GenBank will likely double in size, to over 1 million sequences. The increase will result from the continuation of collaborative projects such as the Merck - Washington University human EST project as well as the startup of a new Howard Hughes Medical Institute/Washington University project for a mouse EST database. These projects which will account for several hundred thousand sequences will become an extremely valuable free and unrestricted resource for researchers to identify and characterize genes responsible for human disease. NCBI will assume the critical role of ensuring that the sequences, which will be generated at the rate of 8,000 per week, are properly entered into the database and made immediately available to the public.

NCBI has taken the lead in a new project PubMed; a collaboration between NLM and publishers of biomedical journals to link MEDLINE to online journals through the World Wide Web. Users will be able to search the entire biomedical literature through Medline and link from a Medline abstract to the corresponding full-text version of an article as provided directly from the publisher. PubMed will furnish health-care providers, researchers and students with more rapid and efficient access to the published literature. Because of its role as a public biomedical information provider, NLM is uniquely positioned to create linkages from the publisher's articles not only to MEDLINE abstracts, but also to gene sequences, protein structures, disease descriptions, and clinical practice guidelines. Publishers have enthusiastically endorsed the PubMed concept since it allows them to maintain their own independent online services while expanding their linkages with other publishers and with government health information sources.

NCBI has developed innovative retrieval systems to provide linkages between the raw sequence data and related scientific literature giving researchers a virtual library to browse. NCBI is adding 3-D protein structure information to the sequence data which can provide

valuable insights into biological function and assist in drug design. Through the Molecular Modeling Database (MMDB) at NCBI, users can identify proteins by using both sequence and structural similarity searching.

With collaboration from major gene sequencing centers, NCBI is producing integrated genetic, physical, and sequence maps of complete chromosomes as well as cross-referencing databases associating human sequences with those of well studied model organisms such as mouse, drosophila, nematode, and yeast. Through use of the World Wide Web (WWW), researchers on the Internet will be able to view complete mapping information from NCBI servers saving hours and days of research time.

NCBI has developed new WWW software (BankIt) for the input of sequences from individual laboratories. The interactive nature of submitting sequence data permits a series of automated checks to be run and feedback from the author to be obtained before the sequence is formally submitted to GenBank. This improves both the quality and timeliness of entries. The quality of the data has also been enhanced through the GenBank Fellows training program which now has 7 fellows selected from an applicant pool of over 200. The fellows' primary responsibility is to improve the quality and annotation of GenBank entries and in the process receive training in bioinformatics.

Through participation in the High Performance Computing and Communications initiative, NCBI is a major worldwide site for gene sequence information. Search techniques developed by NCBI researchers (BLAST sequence similarity search algorithms) have been adopted worldwide as the standard for sequence searching because of their speed and sensitivity. Over 25,000 queries are handled everyday by NCBI computers including thousands of queries which involve computer-intensive comparisons of a single sequence against the entire database. NCBI is recognized as the major international site for comprehensive and fast sequence database searching. Through recent improvements in the BLAST algorithm, NCBI has been able to accommodate an increase in database size and number of searchers without purchasing new hardware, thereby saving an estimated \$300,000 this year. We are also investigating the use of clusters of inexpensive multi-processor PCS to keep search times under a few seconds even for very extensive searches. Through the Internet, NCBI provides researchers not only sequence data but bibliographic information from Medline, as well, which is linked to sequences and the proteins they encode.

NCBI will continue to work with other Federal agencies such as the Department of Agriculture and the U.S. Patent and Trademark Office (USPTO) to ensure that sequence data, respectively, from the Plant Genome Project and in issued patents is included. NCBI collaborates closely with data sources in Europe (European Molecular Biology Laboratory) and in Japan (National Institute of Genetics) to maintain international coverage of gene sequence information.

Finally, NCBI will continue to strengthen its extensive intramural research program in computational molecular biology and play a key role in assisting gene sequencing groups in the analysis and identification of function of newly sequenced DNA and in protein structure

prediction. Senior NCBI scientists work closely with the NIH intramural research program in human genome research as well as with programs at academic institutions where NCBI expertise in sequence analysis has been instrumental in the discovery and analysis of human disease genes.

Toxicology and Environmental Health Information Program (TEHIP)

Twenty-nine years have passed since the Division of Specialized Information Services (SIS) first established the Toxicology Information Program, now known as the Toxicology and Environmental Health Information Program (TEHIP). TEHIP's evolution has kept pace with the spread of, and demand for, toxicological and environmental health information, by taking advantage of new computer and communication technologies. Such mechanisms have enabled SIS to provide more rapid access to a wider audience. The development of novel search capabilities means that users require less prerequisite search knowledge and thus data can be relayed to them more efficiently. SIS is now moving towards the Internet to explore ways to point and link users to relevant sources of toxicological and environmental health information wherever these sources may reside. This will be accomplished through the TEHIP and AIDS Internet Gophers recently made public by SIS, and by a new World-Wide-Web server which will be made publicly available in 1996.

SIS constantly reexamines the scope and coverage of its current programs, proposes new opportunities to enhance its information services, and investigates emerging areas. This examination will continue in 1996 using the mechanism of an Institute of Medicine (IOM) evaluation of the TEHIP Program. Recommendations from the final report of this evaluation will be used in the future development of SIS products.

The Toxicology Data Network (TOXNET) was developed by SIS, and its data banks on the MEDLARS System constitute one of the world's most comprehensive sources of information on the health and environmental effects of hazardous substances. This computer system will continue to offer the following array of services: The Hazardous Substance Data Bank containing data on about 4,500 chemicals whose "exposure potential" is of concern. These data are relevant to human and animal toxicity, biomedical effects, safety and handling, human exposure, environmental fate, and other related areas. The Toxic Chemical Release Inventory (TRI) series of files (TRI87-TRI94), compiled and maintained by the Environmental Protection Agency (EPA), are also made publicly available on TOXNET. TRI contains data collected annually from industry on the amounts of over 362 specified chemicals released to the environment (air, water, land or underground injection). Also included is information on amounts of chemicals transferred to waste sites, and methods used for waste treatment. Source reduction and recycling data are also available beginning with the TRI91 file in compliance with the Pollution Prevention Act of 1990, as well as accidental release of chemicals.

Additional TOXNET data banks are made available through collaborative agreements with other agencies. They include: the Chemical Carcinogenesis Research Information System (CCRIS), a data bank containing published test results from carcinogenicity, genotoxicity, and tumor promotion studies from the National Cancer Institute; the Integrated Risk Information System (IRIS), which contains health risk and regulatory information for both carcinogens and

non-carcinogens and the GENE-TOX file, which contains data on genetic toxicology from EPA; the Registry of Toxic Effects of Chemical Substances (RTECS) from the National Institute of Occupational Health; the Developmental and Reproductive Toxicology (DART) file, a bibliographic database concerned with agents that cause birth defects and infertility, as well as the effects of neonatal and childhood exposure, and the Environmental Mutagen Information Center (EMIC) database which contains citations to the literature on agents that have been tested for genotoxic activity.

SIS also offers chemical and toxicological information on the Elhill portion of the MEDLARS System. It will continue to support and enhance CHEMLINE (Chemical Dictionary Online) which assists the user in searching NLM's bibliographic databases and contains about 1,400,000 records. ChemID (Chemical Identification File) is a separate Online directory which contains 280,000 records and provides a link to selected lists of chemicals maintained by key regulatory and scientific organizations. Data from the European Inventory of Existing Chemical Substances (EINECS), and the Canadian Domestic Substances List (DSL) are also available. TOXLINE and TOXLIT are "toxicology" bibliographic retrieval services, which contain over 3,962,000 records. They use a variety of literature and secondary sources to maximize coverage of the most current toxicological and biomedical literature.

The Directory of Information Resources Online (DIRLINE), is NLM's directory of over 15,000 health and biomedical information providers. These resources include voluntary organizations, NIH-supported scientific resources available for use by other biomedical researchers, and self-help clearinghouses. The database also includes electronic resources such as databases and bulletin board systems covering all aspects of health. In addition to specialized subfiles in areas such as AIDS, maternal and child health, and biotechnology, DIRLINE includes a subfile covering organizations and resources in health services research and technology assessment. DIRLINE is available free-of-charge.

NLM's HIV/AIDS information services continue to grow and mature using the recommendations from the 1993 NIH HIV/AIDS Information Services Conference as the guide for this development. NLM's two collaborative projects with other PHS agencies, the AIDS Clinical Trials Information Service (ACTIS) and the HIV/AIDS Treatment Information Service (ATIS) continue to be very successful. While direct online use of the AIDSTRIALS and AIDSDRUGS databases has stabilized, many other information providers are downloading the data and adding it to their services.

To assist users of these electronic biomedical products, SIS's computer-based training activities now include development of an introductory level toxicology course for use in various university health science curricula. The course was developed for a WINDOWS environment, and takes advantage of this widely available graphical user interface to incorporate color graphics, photography, animation, and audio. It is anticipated that an intermediate module will be added to the course in 1996 for its release to the public.

The SIS World-Wide-Web server was developed to cover all programs in SIS. It will be made public early in 1996. New TEHIP and AIDS Gophers were made public during FY 1995, and have enabled SIS to bring specialized types of information in toxicology, environmental health, and HIV/AIDS to a new and rapidly expanding Internet audience. Documents such as manuals are made available on these servers for electronic transfer to customers all over the United States, and new types of data such as the display of chemical structure will be made available for the first time because of the graphical nature of the World-Wide-Web.

SIS continues its support of the Toxicology Information Outreach Project. The objective of this initiative is to strengthen the capacity of Historically Black Colleges and Universities (HBCUs) to train medical and other health professionals in the use of NLM's toxicological, environmental, occupational health and hazardous wastes information resources. In addition to providing workstations, training and free online access to nine HBCUs participating in a pilot training development project, NLM has collaborated with the Agency for Toxic Substances and Disease Registry (ATSDR) to train representatives from 50 additional schools in the use of NLM's valuable online resources.

National Library of Medicine

Research Management and Support

1997 Authorizing Legislation - Section 301, 465-467 of the Public Health Service Act. 1997 Authorization: Indefinite.

Budget Authority:

FY 1995		FY 1996		FY 1997		Increase or Decrease	
<u>Actual</u>		<u>Estimate</u>		<u>Estimate</u>		<u>Decrease</u>	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
98	\$8,099,000	98	\$7,562,000	97	\$7,562,000	-1	---

Research Management and Support funds the salaries and expenses of the staff who provide for overall administration and direction of the National Library of Medicine programs, including the extramural grant and contract programs. Among functions carried out in this activity are execution of basic administrative services; contracts processing and management; grants management and the scientific direction of NLM's extramural programs, financial and personnel management; coordination of equal employment opportunity activities; direction of NLM's international programs; public inquiries and management of the Library's publications; and operations research. NLM's planning and evaluation activities are also provided for in this activity.

Funding for Research Management and Support during the last five years has been as follows:

<u>Year</u>	<u>Amount</u>	<u>FTE's</u>
FY 1992	\$7,964,000	107
FY 1993	8,095,000	104
FY 1994	7,990,000	101
FY 1995	8,099,000	98
FY 1996	7,562,000	98

Rationale for Budget Request

The FY 1997 budget request for Research Management and Support is \$7,562,000; the same level as FY 1996. Through this activity, NLM will continue to provide efficient and effective administrative support and management, and scientific direction for its programs.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Extramural Programs:						
Grants:						
Noncompeting.....	65	\$13,959,000	87	\$21,842,000	77	\$15,979,000
Competing.....	94	11,279,000	50	5,120,000	79	11,443,000
Subtotal, Grants.....	159	25,238,000	137	26,962,000	156	27,422,000
Contracts:						
Noncompeting.....	8	5,545,000	--	---	8	6,361,000
Competing.....	--	---	8	6,323,000	--	---
Subtotal, Contracts.....	8	5,545,000	8	6,323,000	8	6,361,000
Total, Extramural.....	167	30,783,000	145	33,285,000	164	33,783,000
	FTEs		FTEs		FTEs	
Intramural Programs:						
Library Operations.....	327	47,771,000	327	49,395,000	328	50,453,000
Lister Hill Center.....	77	23,682,000	82	33,103,000	82	35,872,000
Biotechnology Center.....	33	9,692,000	34	9,839,000	34	10,447,000
Toxicology Information.....	30	5,002,000	30	5,093,000	30	5,151,000
Total, Intramural.....	467	86,147,000	473	97,430,000	474	101,923,000
Research Management and Support	98	8,099,000	98	7,562,000	97	7,562,000
Total Budget Authority.....	565	125,029,000	571	138,277,000	571	143,268,000

NATIONAL INSTITUTES OF HEALTH

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Budget Authority by Activity

(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	Actual	FTEs	Actual	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Programs:												
Med'l. Lib. Assistance.	\$15,090		\$15,685		\$16,708		\$17,106		\$17,558		\$452	
PHS 301.....	11,459		12,735		14,075		16,179		16,225		46	
Total, Extramural....	26,549		28,420		30,783		33,285		33,783		498	
Intramural Programs												
Library Operations.....	38,574	360	45,154	334	47,771	327	49,395	328	50,453	+1	1,058	
Lister Hill Center.....	14,142	86	19,488	77	23,682	82	33,103	82	35,872		2,769	
Biotechnology Center...	10,156	37	9,277	33	9,692	34	9,839	34	10,447		608	
Toxicology Information.	4,936	38	4,865	33	5,002	30	5,093	30	5,151		58	
Total, Intramural.....	67,808	521	78,784	477	86,147	473	97,430	474	101,923	+1	4,493	
Research Management and Support												
Support.....	8,038	104	7,797	98	8,099	98	7,562	97	7,562	-1	0	
Total, Obligations.....	102,395	625	115,001	575	125,029	571	138,277	571	143,268	0	4,991	
Unobligated Balance Lapsing												
Lapsing.....	117		236		166							
Total, Budget Authority..	102,512	625	115,237	575	125,195	571	138,277	571	143,268	0	4,991	

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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National Library of Medicine

Summary of Changes

1996 Estimate.....	\$138,277,000
1997 Estimated budget authority.....	<u>143,268,000</u>
Net Change.....	+4,991,000

	1996 Current		Change from Base	
	<u>Estimate Base</u>	<u>Budget</u>	<u>Estimate Base</u>	<u>Budget</u>
<u>Changes:</u>	<u>FTEs</u>	<u>Authority</u>	<u>FTEs</u>	<u>Authority</u>
A. Built-in:				
1. Intramural Programs				
a. Within grade increase.....	\$28,541,000			+\$410,000
b. Annualization of January 1996 pay increase.....	28,541,000			+174,000
c. January 1997 pay increase.....	28,541,000			+673,000
d. Service and supply fund increase.....	1,413,000			+43,000
e. Payment for centrally furnished services.....	10,053,000			+744,000
f. Increased cost of supplies, materials, literature and other expenses.....	57,423,000			<u>+1,723,000</u>
Subtotal.....				+3,767,000
2. Research Management & Support:				
a. Within grade increase.....	6,191,000			+89,000
b. Annualization of January 1996 pay increase.....	6,191,000			+37,000
c. January 1997 pay increase.....	6,191,000			+146,000
d. Service and supply fund increase.....	75,000			+2,000
e. Increased cost of supplies, materials, literature and other expenses.....	1,296,000			<u>+38,000</u>
Subtotal.....				+312,000

Summary of Changes--continued

	<u>1996 Current</u>		<u>Change from Base</u>	
	<u>Estimate</u>	<u>Base</u>		
	<u>FTEs</u>	<u>Budget</u>	<u>FTEs</u>	<u>Budget</u>
		<u>Authority</u>		<u>Authority</u>
B. <u>Program:</u>	<u>No.</u>	<u>Amount</u>	<u>No.</u>	<u>Amount</u>
1. Grants:				
a. Noncompeting.....	87	\$21,842,000	-10	-\$5,863,000
b. Competing.....	50	5,120,000	+29	+6,323,000
Total.....	137	26,962,000	+19	+460,000
2. Contracts.....	8	6,323,000	--	+38,000
3. Intramural Programs.....	473	97,430,000	+1	+726,000
4. Research Management	98	7,562,000	-1	-312,000
and Support				
Subtotal.....				+912,000
Total changes.....				+4,991,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment....	571	571	---
Full-time equivalent of overtime and holiday hours.....	4	4	---
Average SES salary.....	\$113,299	\$118,318	+\$5,019
Average GM/GS grade.....	10.0	10.0	---
Average GM/GS salary.....	45,755	47,782	+2,027
Average salary, grades est. by act of July 1, 1944 (42 U.S.C. 207)....	55,561	58,022	+2,461
Average salary of ungraded positions.....	0	0	---
Personnel compensation:			
Permanent positions.....	\$24,841,000	\$25,942,000	+\$1,101,000
Positions other than permanent.....	2,905,000	3,033,000	+128,000
Other personnel compensation.....	630,000	630,000	---
Special personal services payments.	548,000	548,000	---
Subtotal, personnel compensation.	28,924,000	30,153,000	+1,229,000
Personnel benefits.....	5,782,000	6,093,000	+311,000
Benefits for former personnel.....	26,000	26,000	---
Travel and transportation of persons.	432,000	432,000	---
Transportation of things.....	100,000	100,000	---
Communications, Utilities, and Miscellaneous Charges (23.3).....	2,246,000	2,246,000	---
Printing and reproduction.....	1,258,000	1,258,000	---

	1996 Estimate	1997 Estimate	Increase or Decrease
	-----	-----	-----
Other services:			
Consulting Services.....	\$475,000	\$475,000	---
Other.....	40,251,000	42,081,000	+1,830,000
Purchases from Govt. Accts.....	14,215,000	15,338,000	+1,123,000
Operation & Maint. of Facilities....	271,000	271,000	---
Operation & Maint. of Equipment.....	1,596,000	1,596,000	---
R&D Contracts.....	6,323,000	6,361,000	+38,000
Supplies and materials.....	532,000	532,000	---
Equipment.....	8,884,000	8,884,000	---
Grants, subsidies & contributions.....	26,962,000	27,422,000	+460,000
	-----	-----	-----
Total budget authority by object	138,277,000	143,268,000	+4,991,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Administrative Costs

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase/ <u>Decrease</u>
Personnel Compensation:			
Full-time permanent (11.1).....	\$24,841,000	\$25,942,000	+\$1,101,000
Other than Full-Time Permanent (11.3)....	2,905,000	3,033,000	+128,000
Other Personnel Compensation (11.5).....	630,000	630,000	---
Special personal services payments (11.8)	<u>548,000</u>	<u>548,000</u>	<u>---</u>
Total Personnel Compensation (11.9)....	28,924,000	30,153,000	+1,229,000
Civilian Personnel Benefits (12.0).....	5,782,000	6,093,000	+311,000
Benefits to Former Personnel (13.0).....	<u>26,000</u>	<u>26,000</u>	<u>---</u>
Subtotal, Pay Costs.....	34,732,000	36,272,000	+1,540,000
Travel (21.0).....	432,000	432,000	---
Transportation of Things (22.0).....	100,000	100,000	---
Communications, Utilities, and Miscellaneous Charges (23.3).....	2,246,000	2,246,000	---
Printing and Reproduction (24.0).....	1,258,000	1,258,000	---
Consulting Services (25.1).....	475,000	475,000	---
Other Services (25.2).....	40,251,000	42,081,000	+1,830,000
Purchases from Govt. Accts (25.3).....	13,745,000	14,868,000	+1,123,000
Operation & Maint. of Facilities (25.6)....	271,000	271,000	---
Operation & Maint. of Equipment (25.7)....	1,596,000	1,596,000	---
Subsistence & Support of Persons (25.8)....	0	0	---
Supplies and Materials (26.0).....	<u>532,000</u>	<u>532,000</u>	<u>---</u>
Total Administrative Costs.....	95,638,000	100,131,000	+4,493,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

SIGNIFICANT ITEMS IN THE HOUSE, SENATE, AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Outreach - The House in its reports, page 78, stated, "The Committee supports NLM's efforts toward improving health care information sharing among clinicians, researchers, educators, and other health professionals through the implementation of the national information superhighway, and programs such as Internet. In order to maximize the productivity of these activities, the Committee urges that they be effectively coordinated through the use of medical librarians and other health information specialists."

Action Taken or to be Taken

The Library in conjunction with the 8 Regional Medical Libraries and the 4,000 members of the National Network of Libraries of Medicine (NN/LM), is coordinating with medical librarians and other health information specialists the improvement of NLM's outreach efforts through the information superhighway, and programs such as Internet.

Item

Telemedicine - The House in its report, page 78, stated, "The Committee encourages NLM to continue its investment in telemedicine test-bed networks to evaluate the impact of telemedicine on cost, quality, and access to care. In addition, in a study funded by NLM, HCFA, and the Department of Veterans Affairs, the Institute of Medicine is currently identifying key criteria for evaluation of the impact of operational telemedicine projects. NLM will work with its existing test-bed sites to apply these criteria to its telemedicine projects."

Action Taken or to be Taken

Progress is being made under the dozen High Performance Computing and Communications health care applications contract awards made by NLM. Two areas of common concern of the principal investigators of these projects are how to maintain privacy of medical data and how to evaluate the health care benefits versus the costs of the projects. These two subjects are so crucial that the National Library of Medicine has asked the Institute of Medicine to convene panels to study both privacy and evaluation issues related to telemedicine. NLM plans to supplement several of the telemedicine-related projects in 1996 and, if possible, to make new awards in this crucial area.

1996 Senate Report LanguageItem

Outreach - The Senate in its report, page 107, stated, "The Committee supports the NLM's efforts toward improving health care information sharing among clinicians, researchers, educators, and other health professionals through the implementation of the national information superhighway and programs such as internet. In order to maximize the productivity of these activities, the Committee urges that they be effectively coordinated through the use of medical libraries and other health information specialists. The Committee requests that the NLM be prepared to report on outreach funding and activities planned for fiscal year 1997 during the budget hearings next year."

Action Taken or to be Taken

The Library in conjunction with the 8 Regional Medical Libraries and the 4,000 members of the National Network of Libraries of Medicine (NN/LM), is coordinating with medical librarians and other health information specialists the improvement of NLM's outreach efforts through the information superhighway, and programs such as Internet. The NLM will be prepared to report on outreach funding and activities planned for 1997 during this year's budget hearings.

NATIONAL INSTITUTES OF HEALTH
National Library of Medicine

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Appropriation	1997 Amount Authorized	1997 Budget Request
Research and Title III, Part A Investigation... Section 301	42 421	Indefinite		Indefinite	
National Library Title IV, Part D Medicine..... Section 465-478a	42 286	Such sums as necessary	\$138,277,000	Such sums as necessary	\$143,268,000
Total, Budget Authority.....			\$138,277,000		\$143,268,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation ^{1/}
1988	64,399,000	71,465,000	70,399,000	67,910,000
1989	70,626,000	64,836,000 ^{2/}	70,626,000	73,731,000
1990	78,729,000	83,311,000	80,729,000	82,932,000 ^{3/}
1990 Sequester				-1,071,000
1991	89,916,000	80,725,000	94,416,000	91,408,000
1991 Sequester				-1,000 ^{4/}
1992	100,554,000	99,565,000	100,549,000	99,088,000 ^{5/}
1993	107,561,000	103,923,000	103,923,000	103,639,000 ^{6/}
1994	133,349,000	118,481,000	120,481,000	118,019,000 ^{7/}
1995	135,330,000	123,274,000	127,274,000	125,748,000 ^{8/}
1996	136,311,000	138,277,000	136,781,000	138,277,000 ^{8/}
1997	143,268,000 ^{8/}			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Excludes funds for Medical Library Assistance Act programs not considered.

3/ Excludes enacted administrative reduction of \$379,000.

4/ Excludes enacted administrative reduction of \$980,000.

5/ Excludes enacted administrative reduction of \$1,385,000.

6/ Excludes rescission of \$1,962,000.

7/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research. Excludes enacted administrative reductions of \$271,000, \$2,000 and \$253,000. Excludes rescission of \$445,000.

8/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1996 and FY 1997. A regular appropriation for FY 1996 has not been enacted at this time. The 1996 amounts are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Detail of Full-Time Equivalent Employment (FTE)

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Request</u>
Library Operations.....	334	327	328
Lister Hill Center.....	77	82	82
Biotechnology Center.....	33	34	34
Toxicology Information.....	33	30	30
Research Management and Support.	<u>98</u>	<u>98</u>	<u>97</u>
Total.....	575	571	571

Average GS/GM Grade

1992.....	GS-10.0
1993.....	GS-10.0
1994.....	GS-10.0
1995.....	GS-10.0
1996.....	GS-10.0
1997.....	GS-10.0

Note: Includes FTEs associated with HIV Research Activities. These FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Administration
Detail of End-of-Year Employment

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Request</u>
ES-6.....	0	0	0
ES-5.....	1	1	1
ES-4.....	3	3	3
ES-3.....	1	1	1
ES-2.....	0	0	0
ES-1.....	<u>2</u>	<u>2</u>	<u>2</u>
Subtotal.....	7	7	7
Total - ES Salary....	\$744,526	\$793,093	\$828,226
GS/GM-15.....	25	25	25
GS/GM-14.....	35	35	35
GS/GM-13.....	89	87	87
GS-12.....	148	148	148
GS-11.....	31	31	31
GS-10.....	1	1	1
GS-9.....	30	29	29
GS-8.....	58	57	57
GS-7.....	40	40	40
GS-6.....	27	27	27
GS-5.....	15	15	15
GS-4.....	44	44	44
GS-3.....	17	17	17
GS-2.....	6	6	6
GS-1.....	<u>4</u>	<u>4</u>	<u>4</u>
Subtotal.....	570	566	566

Grades established by Act of July 1, 1944 (42 U.S.C. 207):

Assistant Surgeon General	0	0	0
Director Grade	2	2	2
Senior Grade	2	2	2
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	<u>0</u>	<u>0</u>	<u>0</u>
Subtotal	4	4	4
Ungraded	<u>17</u>	<u>17</u>	<u>17</u>
Total permanent positions	598	594	594
Total full-time equivalent (FTE)			
employment, end of year.....	575	571	571
Average ES level.....	ES-3	ES-3	ES-3
Average ES salary.....	\$107,379	\$110,106	\$113,327
Average GS/GM grade.....	GS-10	GS-10	GS-10
Average GS/GM salary.....	\$42,808	\$43,888	\$45,172



THURSDAY, APRIL 25, 1996.

**NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN
DEVELOPMENT**

WITNESSES

**DUANE ALEXANDER, M.D., DIRECTOR, NATIONAL INSTITUTE OF CHILD
HEALTH AND HUMAN DEVELOPMENT**

YVONNE T. MADDOX, M.D., DEPUTY DIRECTOR

**FLORENCE P. HASSELTINE, M.D., DIRECTOR, CENTER FOR POPU-
LATION RESEARCH**

BENJAMIN E. FULTON, ASSOCIATE DIRECTOR FOR ADMINISTRATION

ARTHUR D. FRIED, BUDGET OFFICER

**HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF
HEALTH**

**DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET,
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Mr. PORTER. The subcommittee will come to order.

We continue our hearings this morning on the National Institutes of Health, beginning with the National Institute of Child Health and Human Development. We're pleased to welcome Dr. Duane Alexander, the Director. Dr. Alexander, it's nice to see you. Would you introduce the people at the table with you and then proceed with your testimony.

INTRODUCTION OF WITNESSES

Dr. ALEXANDER. Yes, Mr. Porter, thank you. I would like to introduce our deputy director, Dr. Yvonne Maddox; our executive officer, Mr. Ben Fulton; our budget officer, Mr. Art Fried; the director of our Center for Population Research, Dr. Florence Hasseltine.

OPENING STATEMENT

Mr. Chairman, the Congress established the NICHD in 1962 to reduce infant mortality, improve maternal and child health, and to address the causes and consequences of birth defects and mental retardation through research. This year we are pleased to mark significant progress in all of these areas. We can report a major reduction in infant mortality in the United States due, in large part, to NICHD research. We have discovered a metabolic error that causes neural tube defects, one of the most serious of birth defects. And NICHD-originated vaccines are bringing us closer to the elimination of Hemophilus influenzae meningitis, once the leading cause of acquired mental retardation in the United States.

The budget request we present to you today will allow us to continue to focus on prevention and make progress in these and other areas, while at the same time permitting funding for the construction of the new NIH Clinical Research Center with facilities de-

signed to take into account the unique needs of children participating in research.

Foremost among our accomplishments is the translation of our research into reduced rates of infant mortality. In 1994, the provisional infant mortality rate dropped 4 percent from the previous year, to an all-time low of 7.9 per thousand live births. This represents a decline of 69 percent, from 25.3 per thousand, since the NICHD was established—one of the greatest improvements in any of our public health measures.

The decline from 1993 to 1994 is a case in point. That 4 percent decrease was due almost entirely to reduced deaths from Respiratory Distress Syndrome—RDS—and Sudden Infant Death Syndrome—SIDS. The drop in Respiratory Distress Syndrome deaths is a clear consequence of two research advances. First, NICHD-supported research indicated that deaths from RDS could be reduced from wider use of corticosteroid treatments administered to a woman in premature labor. A rapid change in clinical practice occurred as a result, with many more premature infants receiving this life-saving treatment. The second factor was increased use of surfactant. For premature newborns, the administration of surfactant to their lungs ameliorates or prevents RDS. The discovery of surfactant and development of it as a treatment came from research supported by NICHD and the National Heart, Lung, and Blood Institute, with subsequent commercial development and marketing by the pharmaceutical industry.

The reduction in deaths due to Sudden Infant Death Syndrome is the first we have ever seen and follows the effective public education campaign called "Back to Sleep" that is designed to change the sleeping position of infants. This campaign is led by NICHD and is based on our research showing a link between abdominal sleep position and SIDS. The "Back to Sleep" campaign has resulted in a major behavioral change, from 80 percent of infants being placed on their abdomen to sleep to 70 percent being placed on their sides or backs, with a consequent drop in SIDS.

The continuing challenge in preventing infant mortality is to reduce the numbers of low birth weight infants. Several new NICHD-supported studies offer this possibility. Researchers have shown that a common condition called bacterial vaginosis plays a role in precipitating premature labor, perhaps accounting for 20 to 40 percent of premature births. Our research has shown that treatment of bacterial vaginosis with specific antibiotics can reduce the risk of a premature delivery, thus finally giving us an effective intervention to prevent this persistent problem.

As I mentioned, for many years the leading cause of acquired mental retardation in the U.S. was brain damage from *Hemophilus influenzae* meningitis. A new approach to a preventive vaccine was successfully developed in NICHD's intramural laboratories. This vaccine that eventuated has been incorporated into the routine required childhood immunization series beginning at age 2 months. Since then the number of cases of Hib meningitis has fallen from around 20,000 a year to less than 100, and the disease is on the verge of elimination. This has resulted in savings of at least \$400 million a year, and has ended the fear of mental retardation, deafness, or death from Hib for our Nation's children.

These same NICHD intramural scientists have also developed a new pertussis toxoid vaccine. It has proved highly effective and remarkably free of side effects, and has been licensed in Sweden and is now awaiting FDA approval. Several other NICHD vaccines against prevalent infectious diseases, including *Shigella* dysentery, a major contributor to infant morbidity and mortality worldwide, are currently undergoing testing.

Another infectious disease of major concern is AIDS. Because AIDS is sexually transmitted, we're bringing our expertise in reproductive biology, physiology, and epidemiology to bear on developing new and improved approaches to concomitant prevention of pregnancy and STDs. In addition to basic studies of the immunology of the reproductive tract to explore how and why sexual transmission of HIV takes place, we are supporting extensive applied research to improve physical barrier contraceptives and develop microbicidal spermicides that will kill HIV and other STD pathogens.

Just as our focus on prevention is important for birth defects and infectious disease, it is important for cognitive and behavioral conditions as well. Learning disability is a prime example. During the past few years, our scientists have identified the core cognitive and neurobiological deficits in reading disability. They have developed tests that identify children likely to have this disability prior to school entry, and effective interventions to prevent reading disability and school failure. These interventions are now being evaluated in the classroom setting. Their importance is underscored by evidence that if effective intervention is not provided by fourth grade, the disability is established and is unlikely to be overcome.

Often, despite our best efforts at prevention, we have to deal with conditions that have already occurred. Our research mission then shifts to prevention of the adverse consequences of that condition. Such is the case with our medical rehabilitation research. We're fostering the development of a new generation of assistive devices of unprecedented effectiveness, durability, safety, and affordability. We are supporting a series of projects, many conducted by small businesses, to provide users of a prosthetic arm or leg with a sense of touch and the ability to distinguish hot from cold. Other projects are devoted to developing advanced forms of assisted mobility, improved means of enhancing limb movement, better bowel and bladder control, and more effective ways of modifying the environment at home or at work.

This year we joyously celebrated the award of the Nobel Prize for medicine or physiology to two NICHD grantees for research providing major insights into the development of birth defects. The Nobelists, Doctor Edward Lewis of California Institute of Technology and Doctor Eric Wieschaus of Princeton, were honored for identifying and characterizing a group of genes that control embryonic development in the fruit fly, an excellent model for early human development. In a sense, this highest prize not only honors these scientists, but also rewards all who have consistently supported biomedical research in the United States. This recognition spotlights the return on the investment of the American people in the NICHD and the NIH.

The fiscal year 1997 President's budget request for NICHD is \$543,441,000. I will be pleased to answer any questions.

[The prepared statement and biography of Dr. Duane Alexander follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Child Health and Human Development

The Congress established the National Institute of Child Health and Human Development (NICHD) in 1962 to reduce infant mortality, to improve maternal and child health, and to address the causes and consequences of birth defects and mental retardation through research. This year we are able to mark significant progress in all of these areas. We are pleased to report a major reduction in infant mortality in the United States, due in large part to NICHD research. We have developed a new understanding of a metabolic error that causes neural tube defects, one of the most serious groups of birth defects. And NICHD-originated vaccines are bringing us close to the elimination of *Hemophilus influenzae* meningitis, once the leading cause of acquired mental retardation in the United States.

The budget request we present to you today will allow us to continue progress in these and other areas. We will continue working to prevent premature labor that often results in delivery of vulnerable low birth weight babies. This budget will support our networks of pediatric and obstetric hospitals across the country to speed clinical trials on important maternal and child health research issues. The construction of the new NIH Clinical Research Center, requested in the NIH Buildings and Facilities budget, will also help further progress by providing facilities that are designed to take into account the unique needs of children participating in research, and to take medical questions from the clinic to the laboratory and back again in a setting that provides ideal training for clinical investigators.

Foremost among our accomplishments is the translation of research supported by the NICHD into reduced rates of infant mortality. An actual decline in deaths is the soundest and most telling measure of success. In 1994, the provisional infant mortality rate dropped 4 percent from the previous year, to an all-time low of 7.9 per thousand live births. This represents a decline of 69 percent, from 25.3 per thousand, since the NICHD was established—one of the greatest improvements in any of our public health measures. NICHD research advances have played a major role in this decline.

The decline from 1993 to 1994 is a case in point. That 4 percent decrease was due almost entirely to reduced deaths from Respiratory Distress Syndrome (RDS) and Sudden Infant Death Syndrome (SIDS). The drop in RDS deaths is a clear consequence of two research advances. First, an NIH Consensus Development Conference endorsed the finding from NICHD-supported research indicating that deaths from RDS could be reduced through wider use of corticosteroid treatments administered to the mother during premature labor. A rapid change in clinical practice occurred as a result of the publicizing of this consensus, resulting in many more preterm infants receiving this life-saving treatment. The second factor was increased use of surfactant, a substance normally produced by the lungs to coat the airways that is not always produced by

premature lungs. For premature newborns, the administration of surfactant to their lungs ameliorates or prevents RDS and has lowered the death rate. The discovery of surfactant and development of it as a treatment came from research supported by the NICHD and the National Heart, Lung and Blood Institute, with subsequent commercial development and marketing by the pharmaceutical industry.

The reduction in infant deaths due to Sudden Infant Death Syndrome (SIDS) is the first we have ever seen and follows the effective public education campaign called "Back to Sleep" that is designed to change the sleeping position of infants. This campaign is led by NICHD and is based upon our research showing a link between abdominal sleep position and SIDS. The "Back to Sleep" campaign has resulted in a major behavior change, from 80 percent of babies being placed on the abdomen to sleep to 70 percent being placed on their sides or backs, with a consequent drop in SIDS. The fiscal year 1997 President's Budget includes funds to continue and expand this campaign with the hope of reaching more families and further preventing SIDS.

The continuing challenge in preventing infant mortality is to reduce the numbers of premature deliveries of low birth weight infants. Premature birth and low birth weight increase the risk for infant mortality as well as mental retardation, cerebral palsy, and other problems. These are costly conditions, beginning with neonatal intensive care in the hospital and often extending through adult life. Several new NICHD-supported studies offer the possibility of preventing premature birth. Recently, for instance, researchers have shown that a common condition, bacterial vaginosis, plays a role in precipitating premature labor, perhaps accounting for 20 to 40 percent of premature births. Our research has shown that treatment of bacterial vaginosis with specific antibiotics can reduce the risk of a premature delivery, thus finally giving us a potentially effective intervention to prevent this persistent problem.

This year, NICHD scientists and their colleagues in Ireland demonstrated a specific genetic metabolic defect responsible for a significant proportion of cases of neural tube defects, such as spina bifida. This metabolic error in a pregnant woman can be overcome by folic acid, explaining the earlier finding that giving folic acid to the woman reduces the incidence of these birth defects. Results of this study helped strengthen the justification for folate supplements that led the FDA to issue a new food fortification requirement for folic acid as a preventive strategy to reduce neural tube defects.

As I mentioned, for many years the leading cause of acquired mental retardation in the US was brain damage caused by *Hemophilus influenzae* type b meningitis (Hib). Despite the availability of antibiotic therapy, brain damage, deafness and death often followed this wide spread infection. A new approach to a preventive vaccine was successfully developed in NICHD intramural labs. That advance eventuated in Hib vaccine being incorporated into the routine required childhood immunization series beginning at age 2 months. Since then the number of cases of Hib meningitis has fallen from around 20,000 a year to less than 100, and the disease is on the verge of

elimination. This has resulted in savings of at least \$400 million each year, and has ended the fear of mental retardation, deafness or death from Hib for our Nation's children.

Although we are past the days when parents lived in constant fear of childhood infections, infectious diseases are still a worldwide problem. We remain vulnerable to new epidemics such as AIDS, as well as to old diseases such as tuberculosis that re-emerge, and we need improved vaccines for other diseases. In responding to this challenge, the same NICHD scientists who used new concepts to produce a Hib vaccine have also developed a new pertussis toxoid vaccine. It has proved highly effective and remarkably free of side effects and has been licensed in Sweden where its recently completed field trial was conducted, and the vaccine is now awaiting FDA approval. This new pertussis vaccine is also acceptable for adults and may help to totally eliminate the disease. Several other NICHD vaccines against prevalent infectious diseases, including *Shigella* dysentery, a major contributor to infant morbidity and mortality worldwide, are currently undergoing testing.

Because AIDS is a sexually transmitted disease (STD), a major preventive strategy to interrupt its transmission is to link contraception and STD prevention. NICHD is bringing the expertise of its research community in reproductive biology, physiology, and epidemiology to bear on developing new and improved approaches to concomitant prevention of pregnancy and STDs. In addition to basic studies of the immunology of the reproductive tract to explore how and why sexual transmission of HIV takes place, we are supporting extensive applied research to improve physical barrier contraceptives and develop microbicidal spermicides that will kill HIV, herpes, chlamydia, and other STD pathogens.

Just as the NICHD's focus on prevention is important for birth defects and infectious disease, it is important for cognitive and behavioral conditions. Learning disability is a prime example. NICHD studies of learning disabilities have provided important insights into the ways that children learn and the conditions that promote or inhibit learning to read. During the past five years, NICHD-supported scientists have identified the core cognitive and neurobiological deficits in reading disability, the most prevalent form of learning disabilities. They have developed tests that identify children likely to have reading disability prior to school entry, and developed effective interventions to prevent reading disability and school failure. These interventions are now being evaluated in the classroom setting. Their importance is underscored by evidence that if effective intervention is not provided before fourth grade, the disability is established and is unlikely to be overcome. Funds are requested in this budget to continue these clinical trials of school-based preventive interventions.

Often, despite our best efforts at prevention, we must deal with conditions that have already occurred. Our research mission then shifts to prevention of the adverse consequences of that condition. Such is the case with medical rehabilitation research, a key component of the NICHD mission. This year when the Olympic Games are held in **Atlanta**, the companion Paralympic Games, which feature athletes with disabilities, will provide a vivid example of the value of such research, showing us how individuals use

assistive devices to allow them not only to function, but even to compete in sporting events. These athletes are representative of the more than 13 million Americans with physical impairments who use assistive technology to improve their functioning in the activities of everyday life and to reduce their dependency on assistance by other people. Drawing upon advances in computer science, communication technology, engineering, and biomaterials technology, NICHD is fostering the development of a new generation of assistive devices of unprecedented effectiveness, durability, safety, and affordability. For example, the NICHD National Center for Medical Rehabilitation Research is supporting a series of projects, many conducted by small businesses, to provide users of a prosthetic arm or leg with a sense of touch and the ability to distinguish hot from cold. Other projects are devoted to developing advanced forms of wheeled mobility, improved means of enhancing limb movement, better bowel and bladder control, and more effective ways of modifying the environment at home or work.

This year we celebrated the award of the Nobel Prize for medicine or physiology to two NICHD grantees for research providing major insights into the development of birth defects. The Nobelists, Dr. Edward B. Lewis of the California Institute of Technology and Dr. Eric Wieschaus of Princeton, are long-term grantees of the NICHD. Dr. Lewis has received research support for 21 years and Dr. Wieschaus, who received his first grant from the Institute in 1969, is currently an NICHD MERIT Awardee. These extraordinary scientists were honored for identifying and characterizing a group of genes that control embryonic development in the fruit fly, *Drosophila*, an excellent model for early human development. In a sense, this highest prize not only honors these scientists, but also rewards all who have consistently supported biomedical research in the United States. This recognition spotlights the return on the investment of the American people in the NICHD and the NIH.

The fiscal year 1997 President's Budget request for the NICHD is \$543,441,000. I will be pleased to answer any questions.

CURRICULUM VITAE

NAME	Duane Frederick Alexander, M.D.
BIRTH	August 11, 1940, Baltimore, Maryland
MARITAL STATUS	Married Marianne Ellis, Washington D.C., June 23, 1963; two children
EDUCATION	Pennsylvania State University, University Park, Pennsylvania, B.S. Degree, Pre-Medical, 1962 Johns Hopkins University School of Medicine, Baltimore, Maryland, M.D. Degree, 1966
INTERNSHIP	Intern and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1966-1967
RESIDENCY	Assistant Resident and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1967-1968
MILITARY SERVICE	1968-1970: Surgeon (LCDR), U.S. Public Health Service, and Clinical Associate, Children's Diagnostic and Study Branch, National Institute of Child Health and Human Development, (NICHD) National Institutes of Health (NIH) Bethesda, Maryland 1971-Present: From Surgeon to Assistant Surgeon General, U.S. Public Health Service
FELLOWSHIP	Fellow in Pediatrics (Developmental Disabili- ties), John F. Kennedy Institute for Habil- itation of the Mentally and Physically Handicapped Child, Johns Hopkins Hospital, 1970-71
LICENSURE	Maryland Board of Medical Examiners
CERTIFICATION	Diplomate, American Board of Pediatrics, 1973
POSITIONS HELD	
1971-74	Assistant to the Scientific Director, NICHD, NIH, Bethesda, Maryland
1974-78	Medical Officer (Staff), National Commission for the Protection of Human Subjects of Biomed- ical and Behavioral Research, DHEW
1978-82	Assistant to the Director, NICHD, NIH
1982-86	Deputy Director, NICHD, NIH
1986-present	Director, NICHD, NIH

PERINATOLOGY RESEARCH BRANCH

Mr. PORTER. Doctor Alexander, you bring us a lot of good news in your testimony this morning. And while we don't, and you don't like to use the word "breakthrough," I think in several instances that you've described to us, you might well call the advances breakthroughs.

I start with a difficult question that is counterpoint to all of that, but I do need an answer to it. The Washington Post recently reported your institute's withdrawal of funding from Georgetown University for an NICHD intramural perinatal research program. This initiative grew out of Senate report language, so we are neutral observers in this situation. On the one hand, we certainly support efforts to protect Federal funds from being misspent; on the other hand, we would be concerned if NICHD personnel and contracting procedures played some role in the problems at Georgetown. Could you take a few minutes and lay out for the record the events leading up to the withdrawal of the contract.

Dr. ALEXANDER. I'd be pleased to do that, Mr. Porter. First, the origin of this project came as a consequence of language in the 1993 NIH Revitalization Act that directed NICHD to establish an intramural research program in obstetrics and gynecology. We set up a gynecology research program in the clinical center on campus, but history had shown us from failures in previous attempts to establish an obstetrics program on campus that that would not work. We were not able to attract patients to that program, and we also were not able to staff it adequately given the constraints in hiring that we had at the NIH. We started this activity then at a time also of hiring constraints. So we were forced to do it with a contract and in an off-campus site and do it in the District of Columbia.

The contract was competed openly, fairly. We had several offers and Georgetown, after a bidding process, was selected as the site. We also had recruited Dr. Roberto Romero to be the chief of this branch, with most of the personnel to be provided under the contract with Georgetown rather than Federal employees.

We got off to a good start initially with this project, but difficulties developed during its early operation phases with problems that we attempted to reconcile but were not able to. When that occurred, we met with Georgetown officials, we tried to, by several different ways, to get the operation going and back on track again. But after several months, we determined that that was not going to be possible. Therefore, we made a decision, a very difficult decision, that we would terminate the activity at Georgetown but we would make a commitment to recompete that contract and start it again.

We gave time to the people at Georgetown to close out the research in an orderly fashion so that the investment in the activities that were ongoing would not be lost. We have been making plans to recompete that contract and award it again to get that effort going again. We have not abandoned our commitment to that perinatal research branch or to this important intramural research activity. The request for proposals for the contract should be issued sometime early this summer, and we would hope to complete that as quickly as possible and get it reestablished.

Mr. PORTER. The Georgetown Project did produce some research during the time it was funded then?

Dr. ALEXANDER. It did.

Mr. PORTER. We understand that both the Inspector General and NIH Office of Scientific Integrity have been investigating the Georgetown incident. What is the status of their work?

Dr. ALEXANDER. Those investigations are ongoing. A report has been submitted to the Office of Research Integrity from an initial investigation. We have not received an Office of Research Integrity response to that report. We also understand from discussions with the Inspector General's office that their investigation is nearing conclusion. There has been nothing disclosed from any of those investigations that has come to our attention that has caused us to change direction or lose confidence in the leadership of that branch.

Mr. PORTER. How much money has been lost either through costs associated with the contract or termination penalties?

Dr. ALEXANDER. I would not say that any money has been lost, because research has been conducted with the funds that have been expended. There has been research published, there has also been research presented at the national meeting of the Society of Perinatal Obstetricians and other obstetrics meetings. So the research has been conducted and reported.

We are still in the process of negotiating with Georgetown officials any penalty clauses that will be involved. What we would hope to do would be to minimize that.

Mr. PORTER. Why wasn't the director of the intramural branch hired as an NIH employee rather than being on loan from a university?

Dr. ALEXANDER. In large part, for salary reasons. Salaries are extremely high for obstetricians and gynecologists, particularly with an international reputation such as Dr. Romero has. At that time, we were not able to go anywhere near the competitive market for the salary of a top rank obstetrician. Since that time, the NIH has obtained title 38 funding authority and we are able to provide a salary in a competitive range. In fact, we are in the process of bringing Dr. Romero on as a full-time Federal employee.

Mr. PORTER. Once NIH has a new Clinical Center, could that be the base of operations for your intramural perinatology program, or would you still have a problem with patient recruitment?

Dr. ALEXANDER. It's our judgment, Mr. Porter, that the problems with patient recruitment would still be prohibitive in trying to establish this in the Bethesda site. We had tried this before and difficulties with recruitment of patients either in the Bethesda area, in terms of obstetricians being willing to give up their patients to the NIH or this research program, or recruiting patients from the District of Columbia to come to the NIH campus, travel that distance, even with the convenience of Metro, made it really prohibitive for establishing it there. So we believe that we are far better off in terms of patient recruitment in establishing it off-site. This is not the only off-site NIH clinical facility, and we believe that we can operate it successfully in the District.

Mr. PORTER. Mrs. Lowey?

TEENAGE PREGNANCY

Mrs. LOWEY. Thank you, Mr. Chairman. Last year, I asked about NICHD's work in the area of teenage pregnancy. In light of President Clinton's focus on reducing teenage pregnancy as a national priority, can you update the subcommittee on your work in this area. Specifically, what have you learned about reducing teenage pregnancy that would be helpful to communities across the country that are trying to tackle this terrible problem? One of the most difficult things we deal with is how do you evaluate programs and where do you have success.

Dr. ALEXANDER. We have approached this problem from a number of different areas. Research from our Demographic and Behavioral Sciences program has helped to document the extent of the problem and factors associated with the likelihood of teenage pregnancy so that we know some of the contributing factors and factors that need to be taken into account in designing effective intervention programs. As part of that program, we are directing an adolescent pregnancy intervention program and violence intervention program with funding support from the Office for Research on Minority Health at seven sites around the country in cooperation with communities and universities. All these projects are developing interventions that are directed toward the dual problems of reducing violence and teenage pregnancy. So those are seven different intervention studies that are underway that should provide good information on ways to develop programs at the community level that will be effective. All of those have very strong evaluation components built into them. As part of our D.C. initiative, there is a teenage pregnancy intervention program that is just getting started in the District of Columbia as well as a parenting improvement program. Both are also being done as a research activity.

So we have a number of programs underway that we hope will serve as models that we can learn from that will help communities to set up activities that will assist them in dealing with their teenage pregnancy problems.

Mrs. LOWEY. These programs, the seven demonstrations you were talking about, have been in existence for how long?

Dr. ALEXANDER. They are now in their third year of operation. They are planned five years.

Mrs. LOWEY. When will they be completed?

Dr. ALEXANDER. They have two more years to run before they will be completed and we will have evaluations.

Mrs. LOWEY. So there's no intermediary information or reports or analysis?

Dr. ALEXANDER. No, there is not. Nothing available from them right now.

CHILD DAY CARE

Mrs. LOWEY. Your institute recently released the results of a major study on the impact of child care on a child's development. Can you please discuss what you concluded about child care and tell us what you learned that would be helpful for working parents who depend upon day care.

Dr. ALEXANDER. Mrs. Lowey, we have an awful lot to learn from that study yet. What was reported was one very important finding from a study that we expect to have very many important findings to be released. This is a study that was initiated by the institute several years ago in response to concerns that a large percentage of our infants were being placed in day care as mothers returned to work, and some concerns had been raised by small studies that suggested there might be an adverse impact on the children's development as a consequence.

This large study of 1,300 families, done at 10 different sites, was organized as a cooperative agreement with the institute and the scientific community. This is the first of many findings to be presented, but it addressed the most important concern that had been raised by previous studies; namely, was there an adverse effect on an infant's attachment to the mother because of the day care experience. It provided reassurance, I think, to working mothers that, in fact, when the mother is attentive and sensitive to an infant's needs, there is not an adverse impact of the day care experience, even when many other factors about the type of day care are taken into account. So there was a lot of reassurance to working mothers from this initial finding.

Future evaluations will deal with cognitive development of the children, their social development and behavioral development, the health impact of day care on children, as well as extending these findings beyond 15 months. This was just one observation at 15 months of age of one particular behavior. We're following these children again at 24 months, 36 months, 4 and a half years, and 7 years of age so that we will have a longitudinal capability of evaluating many different facets of the day care experience in relation to the potential impact on children and families.

Mrs. LOWEY. How many day care sites are included in this study?

Dr. ALEXANDER. There are 10 different sites around the country, but these represent not just one kind of day care site. These are universities and they are looking at different types of child care, including no child care. A part of the sample includes the children of mothers who are at home providing in-home care themselves, part of it is care given by fathers, part by grandparents, part of it is home day care by somebody coming into the home or small numbers of children in a day care site, or group day care. So we're looking at many different types of day care and environments.

Mrs. LOWEY. I'll be interested in following that because from my experience in looking at those studies, and I think the same goes for teenage pregnancy or any juvenile delinquency intervention, there are so many variables, depending upon the warmth of the staff and the attachment of the staff to the child. I have always had real questions about how you can scientifically do any kind of a study in those areas where there are so many variables. In fact, one of the questions I always ask as we fund many of these programs, how do you legislate excellence? I have visited dozens and dozens of intervention programs through the years and usually the successful ones are ones that have a warm, dynamic leader that provides mentoring, love and nourishment to the kids. So I will be

interested in seeing how you control all these variables in order to get any kind of legitimate evaluation.

Dr. ALEXANDER. Mrs. Lowey, your perception is right on target. The evaluations are, in fact, looking at children's interaction with their parents in the home, with observations by psychologists who are doing the study, as well as observations at the site of the day care, looking at exactly the kinds of variables that you mentioned. So that is part of the study.

Mrs. LOWEY. I'll be interested in looking at your research and working with you. Thank you very much, Mr. Chairman.

Mr. PORTER. Mrs. Lowey, we will go back and forth on five minutes, so you will have I think ample opportunity to ask further questions.

PREMATURE BIRTHS AND BACTERIAL VAGINOSIS

Doctor Alexander, you mentioned in your testimony the findings that bacterial infections in the reproductive tract are linked to premature births. Is the major challenge in this situation to persuade doctors to screen for and treat those infections, which tend to be viewed as a minor medical problem? And do you plan to recommend screening guidelines?

Dr. ALEXANDER. We do if the follow-up studies that we have in place show a benefit accrues from being able to detect and treat these infections. These are silent asymptomatic infections. The women are basically unaware that they have them in most instances. So we have to screen in order to detect their presence, in spite of the fact that they are present in 20 to 40 percent of women. We have underway at the present time in our maternal/fetal medicine network a clinical trial looking at screening of pregnant women and treating in a randomized way women who are infected with bacterial vaginosis with metronidazole to determine whether in fact that antibiotic treatment will not only treat the infection, but also result in reduced incidence of premature labor and low birth weight.

If, in fact we are able to demonstrate that, we can convince the practice community I believe of the value of screening all pregnant women for this condition and providing antibiotic treatment. This condition also we believe can go a long way to helping to explain and perhaps modify the racial difference in low birth weight and infant mortality that we see. Most of the discrepancy in black/white infant mortality rates is accounted for by differences in low birth weight. Bacterial vaginosis is considerably more prominent among black women than among white, and we believe that it may hold a part of the key to the reason why premature labor and low birth weight are more frequent among minority women. If that is the case and this treatment is effective, it should be a way that we can go about narrowing the gap, the ratio of black/white infant mortality.

SIDS

Mr. PORTER. Dr. Alexander, let me apologize to you and your staff and the members in the audience here, but the activity going on up front here relates to the omnibus appropriation bill and whether and when it will arrive on the floor of the House and some

of the final details of it. I apologize for that, but it is necessary to talk to staff in order to get the process completed today.

An apparent research breakthrough in SIDS was reported last September that a brain abnormality might affect these infants' ability to breathe properly and avoid reinhaling exhaled carbon dioxide. Is follow-up research being done on this hypothesis? What share of SIDS cases do you think might be related to such a brain abnormality?

Dr. ALEXANDER. This was research supported by the NICHD and done by Dr. Hannah Kinney. Her discovery from examination of brain specimens of infants who had died of SIDS identified a deficiency in nerve cells and in neurotransmitters in part of the brain called the arcuate nucleus. This is an area that has the sensors, the receptors that detect levels of carbon dioxide and oxygen in the blood and presumably alerts the infant who is hypoxic to turn its head aside or change his breathing rate in response in order to raise its oxygen level or lower its carbon dioxide level. This abnormality was present in a number, but not all, of infants who had died of SIDS.

In response to this, we are continuing to fund Dr. Kinney's work. Her grant has just been renewed. Also, we have established and are expanding our brain tissue bank of specimens of infants who have died of other causes as well as infants who have died of SIDS and infants who have died of Rett Syndrome and of conditions associated with mental retardation. It is essential to have these tissues available to researchers who are interested in studying this phenomenon. So we are doing that. We are also trying to develop ways to screen for infants who may in fact have such an abnormality for their inability to respond adequately to elevated carbon dioxide levels.

LOW DOSE ORAL CONTRACEPTIVES

Mr. PORTER. The British and German governments have issued warnings about so-called low dose contraceptive pills and the danger of blood clots. To date the FDA has not followed suit. Do you consider this a safety problem for American women?

Dr. ALEXANDER. The NICHD was very actively involved with the international scientific community and the Food and Drug Administration in evaluating the data from the three different studies that were reported and in developing the U.S. response. First, it is important to recognize that the proportion of oral contraceptives that contain the particular ingredients that were associated with this finding is a very small part of the U.S. market compared to what it is in the European market. It was also felt that the findings were suggestive but were not so strong that a warning was indicated for women in the United States. This was action taken in consultation with the FDA, with the Centers for Disease Control and Prevention, with our own scientists, and we feel comfortable with that decision.

VACCINE FOR STAPH A INFECTIONS

Mr. PORTER. In your testimony before the Senate authorizing committee, you described research to develop a vaccine for Staph A infections, which are becoming resistant to most antibiotics and

are a leading cause of hospital-acquired infections. How soon could such a vaccine be marketed?

Dr. ALEXANDER. It is hard to give a specific answer to that, Mr. Porter. The vaccine has been prepared. It has been done by the same group that succeeded with the Hemophilus vaccine and the pertussis vaccine. This is a conjugate vaccine. It has been demonstrated to be effective in a very small scale. What we need is larger scale studies of this vaccine that would succeed in demonstrating its effectiveness, and interesting a manufacturer in producing this product. So far we have not identified a manufacturer that wishes to develop this vaccine but we are trying to do so.

Mr. PORTER. Dr. Alexander, I apologize, but it is going to be necessary for me to attend a Republican conference on the omnibus appropriation bill. I am going to ask my colleague from Arkansas, Jay Dickey, to take the chair and preside during this time. I don't know whether I will be back before you complete your testimony, but let me personally thank you for the fine job you are doing at the institute and for the exciting news that you brought us this morning about so many breakthroughs and advances in the areas under your jurisdiction.

Dr. ALEXANDER. Thank you very much, Mr. Porter.

Mr. PORTER. Mr. Dickey.

Mr. DICKEY [assumes chair]. Thank you, Mr. Chairman. I yield to the gentlewoman from New York for five minutes.

TOPICAL MICROBICIDES

Mrs. LOWEY. Topical microbicides have the potential to prevent the transmission of AIDS and sexually transmitted diseases. I know your institute is involved in this area of research and development and I would like to ask a few questions about your work. Can you please give us an update on the status of clinical trials for over-the-counter spermicides as microbicides and for new topical microbicide products.

Dr. ALEXANDER. Yes. We're involved in evaluating over-the-counter products now, most of which contain nonoxynol-9, because if they are, in fact, effective microbicides as well as spermicides, they are the most ready at-hand available method for women to use as topical microbicides rather than trying to develop new products which will take some time. Our evaluations of those at the present time involve looking at the duration of action of nonoxynol-9 as both a spermicide and a microbicide, the irritation in the vagina of this product, as well as the role of the vehicle in which nonoxynol-9 is contained in providing adequate coverage and persistence in the vagina. We also are looking at trying to develop different kinds of vehicles or carriers for nonoxynol-9 that will provide less irritation and better coverage and longer lasting effectiveness.

We are also at the same time trying to develop new microbicides. We have several under study in various contract activities. There is one called C31g that is in human trials at the present time. Several nonoxynol-9 oligomers are being readied for clinical trials. And there is another product that is a gel capsule that is a sustained release preparation that we would hope to have available that would provide 24 hour coverage. There are several other products coming along. There is one that involves a substance called

magainins that we believe would be both spermicidal and microbicidal, and we are presently negotiating with the company a cooperative research and development agreement to pursue that work.

Mrs. LOWEY. In fact, that was the follow-up question I wanted to ask. Perhaps you can discuss with us NIH's relationship with industry in terms of topical microbicide product development efforts. Are there obstacles to engaging in effective collaborations with the commercial sector in this effort?

Dr. ALEXANDER. Yes. CRADAs, the Cooperative Research and Development Agreements, have traditionally been primarily intramural mechanisms, where our scientists in the intramural program develop these arrangements with industry. Doing them on the extramural side is a bit new. We are still feeling our way with them. Several have been set up and we are in the process of working out our first CRADA in this particular area. It can be done. It can work effectively. It is new, but I think it is going to provide us with a very effective mechanism for working with industry to develop these products.

ULTRASOUNDS, ANTENATAL STEROIDS, AND MENINGITIS VACCINE

Mrs. LOWEY. Thank you. Your institute has developed several treatments that are not only making a difference in people's lives, but have also demonstrated tremendous cost-savings. I am thinking in particular of your work in the areas of ultrasounds, antenatal steroids, and a new vaccine for meningitis. Can you discuss your research in these areas at greater length.

Dr. ALEXANDER. The Hemophilus influenza vaccine that I mentioned in the opening statement is extremely effective, to the point of virtual elimination of the disease. Calculations of the annual cost-savings from use of this vaccine are approximately \$400 million. The use of antenatal steroids for fetal maturation to try and reduce the incidence of Respiratory Distress Syndrome, intracranial hemorrhage, and necrotizing enterocolitis has proved to be another effective intervention and is one of the factors that has contributed to our reduced infant mortality rate that we reported from 1993 to 1994 and seems to be continuing. The cost-savings that are associated with that, based on our current estimates, are about \$160 million a year due to reduced incidence of Respiratory Distress Syndrome, shorter stays in a neonatal intensive care nursery, and so forth. With diagnostic ultrasound, a study that we supported tried to assess the usefulness of routine diagnostic ultrasound in all pregnancies. That study demonstrated that, at the present time as used in general practice, there was not a detectable benefit from routine use of diagnostic ultrasound in an office practice in terms of reducing the incidence of premature labor or lowering infant mortality. So the recommendation as a result of that study was that this diagnostic ultrasound not be used routinely but only with indications. Again, there were cost-savings implications for that on the order of about \$150 million a year if that were universally adopted.

Mrs. LOWEY. Thank you. Thank you, Mr. Chairman.

Mr. DICKEY. This committee would like to recognize a very special guest, Sarah Riggs. Sarah, would you stand up please. Thank

you for coming. It's "take your daughter to work day." Mr. Riggs is recognized for five minutes.

Mr. RIGGS. I'm going to decline, Mr. Chairman, as much as I would like to question, because I too intend to attend our conference meeting here in just a moment. So I apologize to all the witnesses. This is an important conference meeting, a Republican caucus meeting regarding the omnibus appropriations bill going to the floor later today.

Mr. DICKEY. The more you all talk about having to be there, the more these folks are going to realize that I am still here. [Laughter.]

That I am of no significance. If you can just stay quiet about that, it would be appreciated. [Laughter.]

ANTIPROGESTIN RESEARCH

Mr. DICKEY. Dr. Alexander, I would like to ask you a question, if I may. It is my understanding that the NICHD's contraceptive development branch of the Center for Population Research has sponsored development of a new "morning after" pill called CDB-2914. It is also my understanding that NICHD has claimed the drug not to be for abortion use, but rather for use as a post-coital contraceptive. If the pill is to be used after conception, after establishment of pregnancy, then isn't it indeed an abortion drug?

Dr. ALEXANDER. No, it is not, Mr. Dickey. Our work with this particular compound came out of a program of trying to synthesize antiprogestins for a number of obstetric and gynecological uses. One of the most promising of these was the one termed CDB-2914. It seems to be a very specific antiprogestin without some overflow effects that would have impact on other hormones. We are pursuing use of this as a post-coital contraceptive only. This is a pill that would be used within 24 to 48 hours of unprotected intercourse, and would be intended to prevent pregnancy from occurring. Pregnancy does not begin until a fertilized egg implants, if a fertilized egg does in fact exist. And without a pregnancy in existence, there is no conception and there is no abortion possible. So the intent here is to provide a post-coital contraceptive that is not an abortifacient pill at all. The uses that we are exploring are strictly those.

Mr. DICKEY. You used a word that I'm not familiar with, antiprogestin. What does that mean?

Dr. ALEXANDER. It is a chemical substance that interferes with a hormone called progesterone. Estrogen and progesterone are the primary female hormones that help to regulate the menstrual cycle and the reproductive process. And progesterone is one of the hormones that's essential for establishing pregnancy. Antiprogestins counteract the effect of progesterone; in fact, they block the receptor for progesterone so that it cannot act. And if it cannot act, it cannot prepare the uterus for pregnancy. So in this instance, the antiprogestin prevents a pregnancy from occurring.

Mr. DICKEY. Tell me if you have answered this question already, but in your professional opinion, once CDB-2914 is developed, do you think it could be, or has the potential to be, an effective abortifacient? In other words, do you have reason to doubt that its use would be any different from that of RU-486?

Dr. ALEXANDER. As a member of the class of antiprogestins, it could be used for any potential uses for which other antiprogestins might be used. It is our anticipation that the dosage of the pill required for use as a contraceptive would be far below the dose that would be required for its use as an abortifacient; therefore, we would expect that the marketed pill would be much too insufficient to be used as an abortifacient.

Mr. DICKEY. Please describe the tests that will be performed in the course of phase I and phase II clinical trials of CDB-2914. Is there discussion for NICHD involvement in phase II research?

Dr. ALEXANDER. The phase I studies are dosing studies where we're trying to get an indication at different dose levels of what the effect of this particular compound is. It is monitored by looking basically at endometrial biopsies. Endometrium is the lining of the uterus that the progesterone has an effect on. So the dosing studies will be our phase I studies. Based on that, a dose will be selected for use in phase II. These are still studies in which we will not be testing efficacy, but use in a larger sample of women of this particular pill, again looking at its effect on endometrial lining and on other aspects of the hormonal cycle. They are basically safety studies.

Mr. DICKEY. Will NIH or NICHD plan to have a role in clinical trials after phase I and phase II, and will these institutions or any other Federal institution act to assume any of the liability of the private firm that funds any further clinical trials of CDB-2914?

Dr. ALEXANDER. That depends on what we find, Mr. Dickey. We're not sure that this is going to work, first of all. If it does work, what we would try to do is turn products like this over to industry for the final development phase. If we are successful in that, that would be our intent.

Mr. DICKEY. One last question on my part. If you are free to do so, please identify the licensee of Research Triangle Institute which is planning to commercialize CDB-2914.

Dr. ALEXANDER. I will have to supply that for the record, Mr. Dickey.

Mr. DICKEY. You can?

Dr. ALEXANDER. Yes. I will supply it for the record.

[The information follows:]

LICENSEE TO COMMERCIALIZE CDB-2914

The license to commercialize CDB-2914 is held by BKB Pharmaceuticals, LLC., located in Washington, D.C.

Mr. DICKEY. Thank you, Dr. Alexander. Mrs. Lowey.

Mrs. LOWEY. Thank you, Dr. Alexander, for appearing before us. I have no further questions.

Mr. DICKEY. Thank you, panel. We appreciate your testimony here today.

Dr. ALEXANDER. Thank you, Mr. Dickey.

Mr. DICKEY. You're free to go. [Laughter.]

[The following questions were submitted to be answered for the record:]

AIDS RESEARCH

Mr. Porter: The recent Levine report on NIH AIDS funding recommended a consolidation of the multiple AIDS clinical trial networks supported at NIH. Can you tell us your opinion of this recommendation, and what it would entail for your pediatric AIDS clinical trials?

Dr. Alexander: With regard to the pediatric AIDS clinical trials, it is stated in the Clinical Trials Area Review Panel Findings and Recommendations that, "Although it took time and the firm commitment of the respective Institute Directors, the combined NIAID/NICHHD infrastructure is now established and effective. The unique elements of the combined resources from the two Institutes, with cooperative governance by a program staff from both Institutes, form a single functional unit and constitute a model for other inter-institute collaborative efforts." This panel report authored by more than 20 clinical trials experts from around the world confirms that NICHHD has succeeded in working well within a consolidated clinical trials network for more than six years. It also demonstrates that NICHHD in collaboration with NIAID developed the model for multi-Institute, multi-clinical trials efforts. Thus, the NICHHD has proven that it can cooperate effectively whether there is a separate pediatric network or a consolidated effort.

Mr. Porter: More broadly, the panel suggested a need for rethinking the current pediatric AIDS efforts. As the growth in the number of pediatric AIDS cases slows, should the research response be modified?

Dr. Alexander: In considering this issue, it is essential to remember that there are over 13,000 HIV-infected children in the U.S. at this moment. HIV infection is and will remain for some time a leading killer of children and young people in this country. Thus, the research response must continue to focus on treatment for these children and the thousands who will follow them. The Phase III capacity of the clinical trials group in pediatrics must be maintained. We must also continue to support current efforts to reduce the rate of transmission of infection from pregnant women at disease stages that were not included in the ACTG 076 trial by exploring ways to diminish or eliminate transmission in the women who are most immunocompromised and most likely to transmit. Lastly, we must acknowledge that the preponderance of infection in children is in the developing world. As responsible citizens of the world, we must continue to support research efforts which examine treatment and prevention strategies which will be feasible and cost-effective in developing countries. Fortunately, we had the necessary foresight to anticipate the appropriate research in the face of a success of ACTG 076 and now have appropriate programs in place.

"BACK TO SLEEP" CAMPAIGN

Mr. Porter: Do you plan any new features to your SIDS "Back to Sleep" campaign in 1997?

Dr. Alexander: Our plans for 1997 include new print material geared to ethnic groups. We also plan to produce the training video in Spanish. In planning stages is the design of a stand alone portable table-top exhibit that can be pre-stocked with Back to Sleep material and sent to numerous meetings and conferences throughout the country.

NATIONAL CENTER FOR MEDICAL REHABILITATION RESEARCH

Mr. Porter: How has the National Center for Medical Rehabilitation Research in your Institute defined its role, both at NIH and in the context of rehabilitation research funded by the VA and the Department of Education?

Dr. Alexander: A variety of avenues have been pursued to define the role of the National Center for Medical Rehabilitation Research (NCMRR) vis-a-vis other parts of NIH, the Department of Veterans Affairs, and the Department of Education.

The legislatively defined mission of NCMRR is to conduct and support research and research training relevant to the rehabilitation of people with physical disabilities. As the organizational focus for medical rehabilitation research at NIH, a primary goal of NCMRR is to bring the health-related problems of people with disabilities to the attention of America's best scientists in order to capitalize upon the myriad advances occurring in the biological, behavioral, and engineering sciences.

The Center's mission was elaborated and given specificity in the *Research Plan for the National Center for Medical Rehabilitation Research*. The plan was formulated by The National Advisory Board for Medical Rehabilitation Research that was established in the legislation (PL 101-613) that created the Center. The plan identifies seven emphasis areas that continue to guide development of the Center's program of research. Those areas are:

- improving mobility,
- enhancing behavioral adaptation to disability,
- understanding the body's responses to disabling conditions from an integrated standpoint,
- developing new assistive technology to improve useful functioning,
- improving measurement tools to assess the consequences of irreversible physical impairments,
- evaluating the effectiveness of medical rehabilitation practices, and
- training medical rehabilitation scientists.

Several means are used to develop the NCMRR program in a manner that is complementary with programs that support medical rehabilitation research in other organizational components within NIH, the Department of Veterans Affairs, and the Department of Education. The National Advisory Board for Medical Rehabilitation Research that developed the Center's research plan includes *Ex-Officio* members representing the National Institute on Disability and Rehabilitation Research (Department of Education), the Rehabilitation Research and Development Service (Department of Veterans Affairs) and five NIH institutes. The Advisory Board's twice-yearly meetings provide a forum to review research being conducted or planned by NCMRR and by the organizations represented by the *Ex-Officio* members.

The NCMRR director chairs meetings of the Medical Rehabilitation Coordinating Committee, also created in the legislation that established NCMRR. The Coordinating Committee is composed of representatives of other organizational components of NIH that support research relevant to medical rehabilitation. Meetings of the Coordinating Committee provide opportunities to review ongoing or planned activities including conferences, requests for applications, and program announcements. Additional opportunities for the Center to become cognizant of the activities of related agencies have been provided by NCMRR staff participation in the Interagency Coordinating Committee conducted by the National Institute on Disability and Rehabilitation Research, the National Advisory Board for Injury Control (Centers for Disease Control and Prevention), the NIH Interagency Study of Chronic Pain, and in the Arthritis and Musculoskeletal Diseases Interagency Coordinating Committee which is the responsibility of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Mr. Porter: Are SBIRs a widely used mechanism for the Center?

Dr. Alexander: For FY 1995, NCMRR devoted 13.0% of its extramural budget to SBIR grants. This is proportionally a much larger commitment to SBIR funding than has occurred for many other organizational components of NIH. The emphasis on SBIR funding is consistent with the Center's priority on developing assistive technology to improve the functioning, independence, and health of people with disabilities. Small business enterprises can be particularly effective in developing assistive technology and moving those developments to the market. Examples of that technology include improved prostheses that replicate natural movements; computer-assisted mobility devices, orthoses to support impaired limbs and restore useful movements, programmable electronic stimulation to enable people with paralysis to control their bladder or bowels, and use of brain waves by people with extensive paralysis to control their environment. The Center conducted conferences in 1992 and 1995 to plan a research agenda for assistive technology and to stimulate the needed research, including that appropriate to SBIR grants.

SIDS

Mr. Porter: How much funding does the SIDS Second Five-Year Plan recommend for FY 1997 and how does that compare to your budget request?

Dr. Alexander: The Second Five-Year SIDS Plan recommends \$16,300,000 for SIDS specific research in FY 1997. This recommendation is \$4,600,000 more than the FY 1997 budget estimate of \$11,700,000. We will, of course, fund the highest quality projects with the funds available to us.

RESEARCH CENTERS

Mr. Porter: Identify the subject matter and number of research centers supported in 1996.

Dr. Alexander: The information follows:

<u>Numbers</u>	<u>Subject Matter</u>
15	Mental Retardation
4	Learning Disabilities
7	Perinatal Research
19	Child Health Research
16	Reproductive Sciences
3	Contraceptive Development
2	Infertility Research
<u>11</u>	Demographic and Behavioral Sciences
77	Total

ADOLESCENT HEALTH STUDY

Mr. Porter: What is the FY 1997 and total cost of the adolescent health study?

Dr. Alexander: The adolescent health study is a nationwide, comprehensive study of the complex forces that promote good health and well being for our young people and those forces that put young lives at risk. The FY 1997 estimated cost of this study is \$3.8 million. The total cost of this project is approximately \$25.0 million of which over \$20.0 million will have been expended by the end of this fiscal year.

FUNDING FOR RESEARCH AREAS

Mr. Porter: Identify FY 1995-97 direct (not related) spending for the following: pediatric AIDS (with a separate breakout of funding for clinical trials), sudden infant death syndrome, mental retardation, Rett syndrome, contraception, infertility and fibroids/endometriosis/pelvic inflammatory disease.

Dr. Alexander: The support levels for these research areas follow:

(Dollars in thousands)

	FY 1995 <u>Actual</u>	FY 1996 <u>Appropriation</u>	FY 1997 <u>Estimate</u>
Pediatric AIDS.....	\$43,823	\$45,400	\$45,000
(clinical Trials).....	24,272	24,500	22,500
Sudden Infant Death Syndrome			
(Specific).....	10,639	11,500	11,700
Mental Retardation.	57,708	60,300	61,300
Rett Syndrome.....	1,929	2,000	2,000
Contraception.....	41,573	43,800	44,600
Infertility.....	10,277	10,700	10,800
Fibroids/endometriosis/ pelvic inflammatory disease.....	1,833	1,900	1,900

NATIONAL CENTER FOR MEDICAL REHABILITATION RESEARCH

Mr. Porter: Provide a 1995-1997 mechanism table for the National Center for Medical Rehabilitation Research, including intramural research and RMS.

Dr. Alexander: The support levels for the National Center for Medical Rehabilitation Research by funding mechanism are as follows.

(Dollars in thousands)

	FY 1995 <u>Actual</u>	FY 1996 <u>Appropriation</u>	FY 1997 <u>Estimate</u>
Research Project Grants..	\$10,863	\$13,972	\$14,767
Research Centers.....	---	---	---
Other Research Grants...	1,152	1,350	1,350
Research Training.....	2,543	2,647	2,689
R&D Contracts.....	<u>433</u>	<u>531</u>	<u>494</u>
Total Extramural.....	14,991	18,500	19,300
(SBIR).....	(1,952)	(2,600)	(3,200)
Intramural Research.....	468	500	500
RMS.....	<u>1,590</u>	<u>1,500</u>	<u>1,500</u>
Total.....	17,049	20,500	21,300

PEPTIC ULCERS

Mr. Porter: In 1994, an NIH consensus development conference endorsed the findings that *H. pylori* is strongly associated with peptic ulcers. Was your Institute involved in the research that led to this finding? Are you involved in any public education efforts in this regard?

Dr. Alexander: The NICHD was not involved in research that led to the association of *H. pylori* with ulcers and is not involved in any public education effort in this regard. A recent NICHD project did however, focus on the impact of infection with *H. pylori* on the risk and severity of endemic cholera.

PRIMARY IMMUNE DEFICIENCY DISEASE

Mr. Porter: Earlier this year, the subcommittee heard testimony from representatives of the Jeffrey Modell Foundation, which funds primary immune deficiency research. I understand that NIAID has entered into a collaborative effort with the Foundation to fund research into this disease at a level of \$500,000 a year for five years. How is this collaboration working so far? Have you begun to receive proposals from researchers?

Dr. Alexander: The NIAID has entered into a collaborative effort with the Jeffrey Modell Foundation. The NICHD has also entered into a similar type of collaboration. The NICHD and the Jeffrey Modell Foundation are collaborating to fund investigator-initiated research applications at a level of \$500,000 a year for five years on the "Developmental and Genetic Defects of Immunity." The purpose is to identify the genes and elucidate the molecular and genetic mechanisms which are responsible for the normal and defective development of the immune system; these studies will have important implications for diagnosing, understanding, and treating primary immune deficiencies. The Program Announcement (PA) for this joint initiative was published on February 16, 1996. The application receipt dates are: June 1, October 1, 1996 and February 1, 1997, and the initial awards will be made in FY 1997.

The collaboration has been extremely cooperative and productive. The scientific community is enthusiastic about the collaboration because of the additional financial support from the private sector. The first receipt date for this PA is June 1, 1996. Thirteen direct requests have been made for the PA and four investigators have already expressed their intention to submit proposals for the June or October 1996 receipt dates. It is anticipated that additional proposals will be submitted.

Mr. Porter: Do you see this approach as a means of stretching Federal research dollars that might be replicated by other foundations and associations?

Dr. Alexander: The NICHD would welcome such collaboration with other foundations and associations where appropriate.

INFANT MORTALITY

Mr. Stokes: As you know, each year, I ask you for an update on the progress that has been made with respect to infant mortality. While your statement highlights, and I appreciate the significant contributions the Institute has made to lower the nation's infant mortality rates, I remain concerned about the disparity between minorities and non-minorities. What progress do you have to report on infant mortality since you were here last?

Dr. Alexander: The infant mortality rate in 1994 was 7.9 per 1000 live births or 4 percent lower than the rate of 8.3 in 1993. Provisional data for 1995 through June of that year revealed a further decline to 7.7 per 1000. The disparity in infant mortality rates between blacks and whites has increased, with the black-white ratio increasing from 1.9 in 1960 to 2.4 in 1992.

A major determinant of the infant mortality rate is the rate of low birth weight and of very low birth weight, that is, births less than 2500 grams and less than 1500 grams. There has been a slight increase in the low birth weight rate among whites to 6 percent while the rate among blacks has remained unchanged at 13.3 percent in 1993. The rate of very low birth weight shows marked racial disparities; the rate for whites is 1 percent, Hispanics, 1.1 percent, and blacks, 3 percent.

The continuing decline in the infant mortality among all ethnic groups in this country despite the lack of improvement in low birth weight and very low birth weight rates is due to the effectiveness and the availability of neonatal intensive care to all newborns at risk regardless of ethnic background.

Mr. Stokes: What are some of the major barriers that prevent the Institute from making further progress, and what is being done to eliminate or reduce them?

Dr. Alexander: Lack of progress in reducing the rate of low birth weight and of very low birth weight births is a major problem. One of the major reasons for this lack of progress is our current incomplete understanding of the causes of premature labor and delivery and of the lack of effective interventions to prevent preterm births. Research currently ongoing is investigating the role of infectious agents in the etiology of premature labor. Observational studies have suggested that a condition, referred to as bacterial vaginosis, is associated with an increased risk of preterm labor, and that black women have a higher rate of bacterial vaginosis. This bacterial vaginosis hypothesis is currently being tested in a clinical trial supported by this Institute.

Mr. Stokes: Also, highlight for the record the progress that has been made thus far with respect to reducing infant mortality.

Dr. Alexander: The reduction in the infant mortality rate in the United States has been phenomenal, resulting in the last 24 years in a decline from around 20 per 1000 to

7.7 per 1000 in 1995. This decline has come about despite the persistent rate of low birth weight because of the increasing effectiveness of neonatal intensive care which has resulted in the increasing survival of newborns of low birth weight and very low birth weight. We refer to this as an improvement in the birth weight specific mortality, that is the death rate for infants at a given birth weight. During the last two or three years, a major decrease in infant mortality has occurred in deaths due to respiratory distress syndrome, a condition that typically occurs in very small babies born prematurely. This reduction in deaths due to respiratory distress syndrome is due to a new treatment available in the form of surfactant which prevents respiratory distress syndrome. Another factor that accounts for the decline in infant mortality is the reduction in deaths due to Sudden Infant Death Syndrome which is attributed to a change in sleep position. Both these improvements have come as a result of NICHD supported research.

Mr. Stokes: What major research is supported and conducted by your Institute with respect to infant mortality?

Dr. Alexander: The NICHD has for several years now pursued clinical trials for obstetrical complications around labor and delivery and of treatments of complications in premature infants through its networks of maternal fetal medicine and neonatal intensive care units. Clinical studies undertaken in these networks are addressing multiple issues either directly or indirectly influencing infant mortality. These studies are concerned specifically with the prevention of low birth weight (LBW) infants and their management. The LBW infants account for a disproportionately large share of infant mortality. Currently more than 270,000 LBW infants are born annually in the U.S. with 48,000 considered "very low birth weight" (less than 1500 grams). The goal of this overall research, including preterm labor and birth, is to reduce the risk of a child being born with a low birth weight, and not mature enough to adapt successfully to the external environment.

In addition to research supported under its clinical trials network, the Institute has a considerable portfolio of research grants which support investigations of determinants and biomarkers of premature labor and delivery.

Also, within the District of Columbia, the Institute has, over the last three years, been engaged in a collaborative project with six medical institutions in D.C. to address the high infant mortality in that city. A series of projects are currently ongoing which involve collaboration between scientists from these D.C. institutions and the NICHD which focus on several factors which are thought to be directly or indirectly associated with infant mortality in inner city populations.

The Institute also has a large effort directed at research on Sudden Infant Death Syndrome (SIDS). Our activities in this area are described in detail in an answer that follows.

Mr. Stokes: How much is included in the FY 1997 budget for this initiative, and how does it compare with FY 1996, and FY 1995?

Dr. Alexander: The FY 1997 estimate for infant mortality is \$89,900,000. This compares to \$88,400,000 in FY 1996 and \$84,618,000 in FY 1995.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: What progress do you have to report this year with respect to activities underway at your Institute that are designed to address the gap in minority health? Also, provide a more detailed response for the record, be as specific as possible.

Dr. Alexander: Disparities in minority infant mortality, immunization, and perinatal HIV infection and mortality rates are a few of the key areas in which the NICHD has a significant research portfolio. The problems and highlights of research efforts and progress to date are outlined below.

Infant Mortality: Between 1960 and the early 1980s, the infant mortality rate for black infants was 1.9 times higher than that for white infants. By 1993, the disparity had risen to 2.4 times higher for black infants than for white infants. Premature births, respiratory distress syndrome (RDS), and Sudden Infant Death Syndrome (SIDS) are major causes of infant mortality that add to the black-white disparity. The NICHD supports major research efforts in these areas, particularly targeting overall research to improve birth outcomes, starting before pregnancy and continuing through the first months of life.

Progress: The Institute's overall research efforts in infant mortality rates have been quite successful. In 1994, the overall U.S. infant mortality rate dropped 4 percent to an all-time low of 7.9 per thousand live births. This decline was almost due entirely to reduced deaths from RDS and SIDS. The drop in RDS clearly stems from two, previous NICHD research advances. First, NICHD-supported research indicated that deaths from RDS could be reduced through wider use of corticosteroid treatments administered to a woman in premature labor. A relatively rapid change in clinical practice has occurred with many more preterm infants receiving this life-saving treatment. The second factor was increased use of surfactant. For premature newborns, the administration of surfactant to their lungs ameliorates or prevents RDS. The discovery of surfactant and its development as a treatment came from research supported by the NICHD and the National Heart, Lung and Blood Institute, with subsequent commercial development and marketing by the pharmaceutical industry.

Also within the past year, infant deaths due to SIDS have dropped for the first time since they were recorded. This decline follows the effective public education campaign called "Back to Sleep" that is designed to change the sleeping position of infants. This campaign is led by NICHD and based upon our research showing a link between abdominal sleep position and SIDS. The "Back to Sleep" campaign has resulted in a

major behavior change, from 80 percent of babies being placed on the abdomen to sleep, to 70 percent being placed on their sides or backs. While data are preliminary and not disaggregated by race or ethnicity, minority populations are at greater risk for SIDS, with SIDS rates among blacks being two-times that of whites and three- to four-times greater for some Native American/Alaskan Native populations.

To understand better the risk factors for premature and low weight birth, the NICHD launched a study which recently showed that the presence of a common vaginal condition during pregnancy, bacterial vaginosis, plays a role in premature labor, perhaps accounting for 20 to 40 percent of premature births. Of the women enrolled in the study, black women were significantly more likely to test positive for bacterial vaginosis. This observation is in contrast to two other previous studies that found no racial differences in infection rates. However, in many U.S. studies, black women exhibit higher rates of premature birth than do white women, even after correcting for all known socioeconomic and demographic variables. The higher rates of bacterial vaginosis found in black women in this study may help explain higher rates of premature births in this population. Given few and recent studies on this subject, more research is needed to understand better the association between the disparity in premature birth rates among various races and the incidence of bacterial vaginosis, and whether treatment would reduce this disparity.

To understand the disparities, it is also important to examine factors associated with the well-being of mothers and infants and to test the effectiveness of interventions in reducing high infant mortality rates. The NICHD is supporting one such project through its *Community-Based Perinatal Studies and Interventions to Reduce Infant Mortality in Minority Populations*, which is based in Washington, D.C.. Over the past year, several specific projects have been started, including one to obtain detailed information on the content of neonatal intensive care and the qualifications of the care providers in eight Washington, D.C. institutions that provide intensive care to high risk newborns. This study should provide information to determine differences in neonatal survival that may be related to the content of neonatal intensive care as currently offered.

Childhood Immunizations: Nationally, in 1992 and 1993, 10 percent fewer black children (under 3 years of age) received the recommended doses of DPT, polio, measles and Hib vaccines than white children in the same age group. The disparities, however, will differ by city or geographic area. In Washington D.C., for example, only 50% of children under the age of 2 are fully immunized. Being up-to-date on these basic childhood immunizations is one of the easiest ways to ensure that children have equal opportunity to grow up free of many preventable diseases that may have life-long consequences.

Progress: One way to increase the number and percentage of children being vaccinated is to ensure that vaccines continue to be improved, minimizing their chance

for any adverse side effects. The NICHD has and continues to make important contributions to this area.

For example, in the past, brain damage caused by *Hemophilus influenzae* type b meningitis (Hib) was the leading cause of acquired mental retardation in the U.S. The Institute's intramural laboratories helped to pioneer a new and improved Hib vaccine that has been successfully incorporated into the routine, required, childhood immunization series beginning at age 2 months. Since the vaccine was introduced, the number of cases of Hib meningitis has fallen from around 20,000 a year to less than 100. Newest data show that the disease is on the verge of being eliminated in this country. The reductions in new cases result in savings of at least \$400 million each year, and has ended the fear of mental retardation, deafness or death from Hib for our Nation's children.

These same NICHD intramural scientists have developed a new pertussis toxoid vaccine. It has proved highly effective and remarkably free of side effects. Newly licensed in Sweden, it awaits FDA approval. Several other NICHD vaccines are currently being tested against prevalent infectious diseases, including *Shigella* dysentery, a major contributor to infant morbidity and mortality worldwide.

Besides improving the vaccines themselves, another means to increase immunization rates is to develop interventions that encourage parents to seek appropriate well-baby care for their infants. As part of its continuing progress in its Washington D.C., community-based, research effort, NICHD scientists recently started a project to isolate the factors that contribute to the low immunization rates among children less than two years of age, since only about 50 percent of them are fully vaccinated. The results of this study will be used to design and implement an intervention to improve immunization coverage.

HIV Infection and AIDS: According to the Centers for Disease Control, "the AIDS epidemic is shifting from whites to minorities, especially blacks and Hispanics. In 1995, for the first time, the (overall) proportion of persons reported with AIDS who are black was equal to the proportion who are white." In 1995, blacks and Hispanics represented the majority of AIDS cases among men (54%) and women (76%). In addition, the reported AIDS incidence rate among blacks was 6 times higher than among whites, and 2 times higher among Hispanics than among whites. For children, the disparity was even greater: In 1995, 84 percent of children reported to have AIDS were black or Hispanic. Compared to white children, AIDS rates were 16 times greater among black children and 6 times greater among Hispanic children.

Progress: The NICHD is one of the leading institutes trying to find new and improved means to *prevent* disease transmission and progression, especially among women, children and adolescents -- populations that, as noted above, have a disproportionate share of minority individuals with HIV infection. The NICHD targets much of its clinical AIDS research activity on evaluating anti-HIV therapies, as well as

therapies against opportunistic infections in HIV-infected children and therapeutic interventions to prevent perinatal transmission of HIV from mother to child.

The Institute has had many singular and collaborative projects seeing progress in the recent past. The clinical trial ACTG 076, co-funded with the NIAID, showed that AZT given during pregnancy, labor, and for a short term to the newborn, can significantly reduce perinatal HIV transmission. Other NICHD-supported and collaborative studies have shown that 1) Vitamin A and micronutrient supplementation can reduce perinatal transmission and help slow HIV progression in children, 2) treatment with intravenous immunoglobulin can significantly reduce bacterial and viral infections and hospitalizations, while slowing CD4+ (blood cell) count declines in infected children; and 3) the use of ddI and combination ddI/AZT can improve clinical outcomes when used as initial therapy in HIV infected children.

With the growing AIDS epidemic among women, the NICHD is targeting some of its AIDS research on rapidly increasing the number of options available for preventing both sexually transmitted disease and pregnancy. This includes expanding its effort to develop and improve new and existing chemical barriers that can either kill or incapacitate both virus and sperm. These types of barriers are particularly important in protecting women because the female partner can often control their use. Researchers are also concerned that use of hormonal contraceptives may influence the risk of HIV infection among women. In some of their first studies, NICHD-supported investigators were able to use an animal model to show that monkeys given the hormone progesterone were more likely to become infected with a virus similar to HIV than monkeys not given the hormone. While it is still too early to know if this animal study will hold true in humans, the study will help determine the direction of future research in the area.

VACCINE RESEARCH

Mr. Stokes: What is the Institute's role in the development of vaccines, is it a collaborative role with other Institutes, explain?

Dr. Alexander: The outstanding vaccine development program of the NICHD is led by Dr. John Robbins, the chief of the Institute's intramural Laboratory of Developmental and Molecular Immunity. Dr. Robbins and his research team have developed a number of effective new vaccines, especially those that protect children and infants. For years NICHD scientists have collaborated on the development of vaccines with investigators of other NIH institutes, in particular, the National Institute of Allergy and Infectious Diseases, which is the lead institute in vaccine development.

Mr. Stokes: What is the status of the pertussis vaccine, and what other major vaccine research and/or development initiatives are underway at the Institute?

Dr. Alexander: I am very pleased to report, Mr. Stokes, that the clinical trials of NICHD's new pertussis vaccine have been completed and the encouraging results have been submitted to the FDA for approval to take the vaccine to the market. We hope that approval will come in the near future. The vaccine has recently been licensed in Sweden, a country that has been besieged by a pertussis epidemic. The field testing of NICHD's new pertussis vaccine showed it to be effective, and importantly, to have far fewer side effects than the vaccines currently on the market.

NICHD's scientists are continuing to make rapid progress in the development of a number of other major vaccine initiatives, including: 1) conjugate vaccines against *Meningococci* group A, B, and C meningitis and against septicemia are being prepared for Phase I studies; 2) Phase I clinical trials have been initiated to test a new vaccine against *Streptococcus* group B neonatal sepsis; 3) another Phase I clinical trial is underway to test a new vaccine against *Escherichia coli* 0157 enteritis, an increasingly frequent and serious intestinal infection in U.S. children; 4) the Institute is conducting Phase II trials of newly developed vaccines against *Shigellae*, which are common and serious causes of dysentery worldwide, especially in developing countries; 5) NICHD scientists developed, and recently completed Phase II trials of the first vaccine against *Cryptococcus neoformans*, a fungal infection that causes meningoencephalitis in approximately eight percent of AIDS patients; and 6) the Institute's scientists have underway Phase III clinical trials of a new vaccine against *Vibrio cholera*, an organism that is reappearing in South and Central America, in addition to its traditional presence in Asia.

SUDDEN INFANT DEATH SYNDROME (SIDS)

Mr. Stokes: I am encouraged by the progress being made in sudden infant death syndrome research. Now that we have reached this "place of hope," what major research and outreach initiatives are planned for FY 1996, and FY 1997?

Dr. Alexander: The information follows.

Activities in FY 1996

In FY 1996, the NICHD will continue to support its active research project grant program into the etiology, pathogenesis and prevention of SIDS. In addition, some existing studies/initiatives are being extended and expanded in order to maximize the information obtained for the investment.

- o extension of studies funded under RFA HD-91-02, "Event Recordings of High Risk Infants on Apnea Monitors". In Fiscal Year 1991, a multi-center network of clinical sites and a data coordinating center were established to investigate the maturation of cardiorespiratory control in infants on home apnea monitors. Infant health and behavioral states are being correlated with physiologic parameters that place an infant at risk for sudden death. During the first funding

period the study protocol was developed, a new infant monitor was developed and the study was implemented. In order to achieve the targeted enrollment, study proposals have been submitted and will be reviewed for an extension of funding for up to an additional five years.

- o extension of the "Chicago Infant Mortality Study", a case-control study of sudden unexpected infant deaths in Chicago, Illinois, being conducted in collaboration with the Centers for Disease Control and Prevention (CDC). This study is being extended to increase the number of cases for analyses of how behavioral, medical, and environmental factors, (such as smoking, infection, sleep position), interact to further increase the risk for SIDS. In addition, more cases will facilitate the study of sudden deaths that occur at low frequency such as those attributed to accidents, neglect, and abuse. The first funding period of this study has successfully described the behavioral, social and environmental risk factors for SIDS in this inner city, predominantly black population.
- o increasing the catchment of a case-control study of SIDS to include all births within 10 counties representing Northern and Southern California. It is anticipated that 400 SIDS cases and 800 living control infants will be enrolled within the study period. The objectives of the study are (1) to determine the risk of SIDS associated with sleeping in prone, side or back sleeping positions among different racial/ethnic groups (2) to identify risk factors that modify the association of sleeping position with SIDS risk, or become more important as the prone sleep risk is eliminated.
- o extension of the "Infant Mortality Study in the Aberdeen Area of the Indian Health Service (AAIHS)" to extend enrollment through FY 1997. This study, which is being conducted in collaboration with the IHS and CDC, investigates causes of, and risk factors for, the high rate of infant mortality in the AAIHS. Deaths diagnosed as SIDS dominate the infant mortality statistics in the Aberdeen Area, with a rate three times that of the remaining population in North and South Dakota. Neuropathologic specimens have been collected since the study's initiation. Investigations into brain abnormalities, including those recently observed in other SIDS populations, will begin in FY 1996 and continue through FY 1997.
- o "Back to Sleep" - This national public education campaign is in its second year. Since the beginning of the campaign, an increase to 70% has been observed in the proportion of infants under seven months of age who are sleeping on their back or side. The National Center for Health Statistics reports a declining SIDS rate, with the preliminary rate for the first half of 1995 below 1/1000 live births. This year, activities will focus on developing new materials that are culturally acceptable for reaching minority populations, and developing new strategies to reach fathers and grandparents. A major effort will be spent on increased

participation at national meetings to promote the Back to Sleep message and to disseminate campaign materials.

Activities in FY 1997

Expansion of on-going projects:

- o extension of the prospective "Infant Care Practices Study" which is evaluating care-taking practices from birth through one year of age in two geographic areas. This study documents infant sleep position and other risk factors, such as bedding, feeding patterns, well and sick visits, and smoking over time. It correlates these factors with sociodemographic characteristics, examines the reasons for and predictors of changes in behavior, and assesses specific health outcomes. This project provides information to improve the efficacy of the "Back to Sleep" campaign.
- o extension of the national longitudinal study of households, physicians, and hospitals correlating prevalence of infant care practices with SIDS rates over time to continue follow-up through 1998. Infant care practices include, but are not limited to, sleep position, bedding, coverings, and environmental temperature.
- o "Back to Sleep": to continue and improve the efficacy of the public health education campaign, resources are needed for printing and distributing educational materials, supporting the campaign with the telephone information line; targeting minority groups, educating fathers and grandparents, and for evaluating the delivery and acceptance of the strategies used to change the behavior of caretakers.

New Initiatives:

- o Community Child Health Research Network: A network of community based centers will be established in communities with a substantial under-represented minority population, to develop and implement common biomedical research protocols, and to train minority researchers. Specifically, these studies are to determine 1) the prevalence, etiology, and pathogenesis of SIDS and other causes of infant mortality that originate before and after birth in the defined populations; 2) the prevalence, etiology, and pathogenesis of infectious diseases before and after birth that compromise child development; and 3) how available health resources manage these problems.
- o a prospective study to validate potential predictive biologic tests for SIDS risk, such as computer analysis of heart rate variability and cry characteristics in the

general population. This study will build on recent knowledge we have gained on the structure and function of the autonomic nervous system in SIDS infants.

- o studies to increase our knowledge of the infant's immune response to infection, and how microbial toxins and the immune response affect the function of the infant's autonomic nervous system. These investigations will facilitate the understanding of how infants may become vulnerable to SIDS upon infection.

INFANT MORTALITY RANKING

Mr. Stokes: With respect to infant mortality, what is the United States' ranking, and how does it compare to other countries, include a listing for the record.

Dr. Alexander: The most recent year for which data is available for all the applicable nations is 1992. The information follows.

Infant Mortality by Nation

1992 Rank	Country	1992 Rate
1	Japan	4.53
2	Hong Kong	4.81
3	Singapore	4.90
4	Finland	5.16
5	Sweden	5.19
6	Norway	5.87
7	Northern Ireland	5.98
8	Canada	6.10
9	Germany	6.17
10	Netherlands	6.29
11	Switzerland	6.41
12	Denmark	6.51
13	England and Wales	6.58
14	Ireland	6.67
15	France	6.82
16	Scotland	6.82
17	Australia	6.91
18	Spain	7.19
19	New Zealand	7.31
20	Austria	7.53
21	Italy	8.19
22	UNITED STATES	8.52
23	Greece	8.56
24	Portugal	9.29
25	Israel	9.43

LEARNING DISABILITIES

Mr. Stokes: Do we have a good handle on what direction we need to take with respect to furthering progress in unraveling the causes, identifying prevention mechanisms, and developing early detection techniques for learning disabilities? How does the Institute go about translating and disseminating the knowledge gained from disability research to the classroom, to parents, to teachers, and the general public?

Dr. Alexander: The Institute has made great strides during the past decade, and particularly within the past five years, in identifying the causes and developmental course of learning disabilities (LD). We now know that to determine the causes of different types of LD, children must be studied longitudinally, and these studies must be initiated before the youngsters enter school and before they are diagnosed by school personnel. Diagnostic practices employed by school personnel typically vary from state to state and even from school to school. This variability negates any chance of replication of findings and degrades the possibility that findings from one group of children will generalized to another group.

To improve this type of research practice, the NICHD has become a leader in the use of prospective, developmental, longitudinal research studies, where the same children are repeatedly observed and studied over time. The advantage of this research approach is that children are initially identified during preschool or the first grade without having to wait for a diagnosis (typically biased) from school personnel. The children are then studied for several years within a wide range of cognitive, language, academic, neurobiological, and genetic contexts. In essence, the Institute's development and use of this type of research design has allowed NICHD scientists to test clear hypotheses about which classification systems and which definitions are the most valid for LD.

These prospective longitudinal studies of LD have achieved a number of critical goals. These include identification of the cognitive, academic, and behavioral characteristics of children with LD that may be manifested in different ways at different ages and/or developmental periods; identification of neurobiological and genetic features that can help predict different types of LD (specifically reading disability or dyslexia), development of valid early predictors for reading disability; mapping of the developmental course of reading disability; and the assessment of different types of treatments for reading disability.

In sum, during the past decade, the Institute's research program in learning disabilities has provided the field with the first operational definition of reading disability (the most frequent type of LD), has identified the causes of most forms of reading disability, has developed measures to identify reading disability in kindergarten and first grade, has begun to understand better the genetic and neurobiological reasons that reading disabilities occur, and has begun to develop treatment approaches that can

reduce the impact of reading disability on a youngster's life in school and society. During the next five years, the Institute will study other types of LD in mathematics, written expression, and social behavior. Of continuing critical importance is our need to understand the specific genetic and biological factors that predispose children to LD and the Institute's initiatives in neuroimaging are being expanded over the next five years. Likewise, we are now in a position to develop preventive methods for youngsters at-risk for LD and treatment methods for the many older children who continue to face substantial difficulties learning in school. Because of this, a number of new treatment studies are being planned.

The Institute is engaged in a comprehensive effort to disseminate critical research findings to all parents, teachers, policy-makers, and to the children themselves. At the policy level, Institute staff have helped to develop the Interagency Committee on Learning Disabilities which includes members from the Departments of Education, Health and Human Services, Labor, Justice and the White House Council on Disability. This committee meets at least monthly and develops dissemination strategies for all constituents in all agencies. This effort reflects the first time that an integrated research dissemination plan for learning disabilities has been developed and carried out at the federal level. Staff from the Institute frequently provide detailed overviews of the research findings to state legislatures that are involved in insuring that the educational practices in their state build on critical and current research information. Staff are now working closely with legislators in California and Texas. Institute staff are in the field at least four days per month presenting the research findings to parents and teachers. Within the past year, parents and teachers in Kentucky, Virginia, Michigan, Colorado, California, Massachusetts, Texas, Maryland, Florida, Washington, D.C., Washington State, Oregon, Maine, New York, Connecticut, Vermont, Arizona, New Hampshire, Georgia, Pennsylvania, and Louisiana have received research briefings.

PULMONARY HEMORRHAGE IN INFANTS

Mr. Stokes: There have been over 25 cases of infant pulmonary hemorrhaging in Ohio, over 10 in Illinois, and 1 or 2 through the rest of the country. This disease is thought to be caused by a mold that grows in stagnated water, like that which can accumulate in the basement of older homes. What can you tell us about this disease, and is it a new disease or one that is resurfacing?

Dr. Alexander: Neonates who are severely ill with respiratory disease may exhibit bleeding at birth or during the acute phase of their disease. However, they are not classified as "infant pulmonary hemorrhage", and the complication does not occur as a cluster in a specific geographical area. Some infants with the rare diagnosis of idiopathic pulmonary hemosiderosis can die suddenly from pulmonary hemorrhage. Because of the number of cases occurring in Ohio, CDC sent an investigative team which obtained cultures for a fungus (*stachybotrys*) from the homes and this is under study. Presently the results are pending and the attribution of causality is not confirmed.

NOBEL PRIZE

Mr. Stokes: I understand that two researchers supported by your Institute have been awarded the Nobel Prize. According to your opening statement, the award is under the medicine and physiology category. The Institute must be especially proud of these researchers and their achievements. Please, tell us what their work has meant to progress in child health research, and its implications in improving health?

Dr. Alexander: The National Institute of Child Health and Human Development is, indeed, very proud to have had a role in supporting the research of Drs. Edward Lewis and Eric Wieschaus on genetic mechanisms controlling embryonic development. Their work has made us more aware of the intricate genetic networks regulating the turning on and off of genes at specific times and in precise locations within a developing embryo. The discovery of "master control genes" gives us a better understanding of the processes involved in normal development but also has shown that a defect in a regulatory gene can cause birth defects.

Birth defects represent the leading cause of infant mortality in the United States and have an enormous physical and emotional public health impact. Our lack of understanding regarding the etiology of birth defects is further complicated by our elementary understanding of the basic, underlying mechanisms associated with development. The work for which these investigators received the Nobel Prize laid the ground work that others have built upon and has increased our understanding of developmental processes. While Lewis and Wiechaus used the fruit fly, *Drosophila*, in their research, it is now known that the same mechanisms and genes are present in vertebrates, including humans. Consequently, their work on lower organisms is now making it possible for significant advances in understanding the pathogenesis of human birth defects.

Basic studies on flies and mice will improve our insight into the mechanisms of development, facilitate the identification of critical developmental periods, and enable us to verify the genetic and environmental miscues that give rise to such conditions as neural tube defects and skeletal abnormalities. As more genes are identified and associated with the causes of birth defects, these basic studies ultimately may lead to the improvement of early diagnostic procedures and the development of gene therapies to ameliorate or prevent birth defects.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum. What are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Alexander: The most significant outreach and public education activity currently underway at the NICHD is the Back to Sleep program, which was described in a previous question related to Sudden Infant Death Syndrome (SIDS). The goal of this program is to have babies placed on their backs or sides when they are put to sleep, rather than placed in their stomachs. This extensive public health education campaign includes the preparation, printing and distribution of educational materials, a 1-800 telephone information line, and participation at national meetings. Other significant information activities focus on Institute-sponsored conferences and workshops, with follow-up press conferences and press releases, as well as additional press releases for basic and clinical research advances, and extensive informational pamphlets, brochures and reports. The FY 1997 budget includes \$940,000 for all outreach and public education activities, the same level as FY 1996. The FY 1995 amount was \$1,150,000 and in FY 1994, \$1,290,000.

Mr. Stokes: In most of the Institutes, these programs are funded in research management and support account, is this the case in your Institute? If yes, have you been able to maintain these programs in spite of the funding reduction in this budget account? In which outreach areas are you hurting the most?

Dr. Alexander: Yes, these programs are funded within the NICHD research management and support (RMS) budget mechanism. As you can see from the prior answer, these activities received more funding in FY 1994 and FY 1995 than is planned for FY 1996 or FY 1997. We have cut down on the number of publications we can produce, and the number of meetings, conferences and workshops that the Institute can support. The most critical programs, such as Back to Sleep, will continue to get their important messages to the public.

AIDS

Mr. Stokes: With respect to the use of AZT to prevent perinatal transmission of HIV from mother to child, can you tell us what major research activities are underway? Also, what other treatment and transmission prevention avenues are being pursued, by the Institute?

Dr. Alexander: Following up on the 1994 success of AZT in preventing mother to child transmission of HIV shown in clinical trial ACTG 076, the NICHD/NIAD-funded pediatric trials group, in collaboration with NHLBI, is evaluating whether therapy with an HIV-antibody enriched immune globulin (hyperimmune HIV immunoglobulin, HIVIG) combined with AZT will be successful in further reducing mother-to-child transmission in women with advanced HIV infection. This trial, ACTG 185, has currently enrolled more than 300 of the planned 800 mother-infant pairs, and is ongoing. A number of other, smaller clinical trials are also being conducted to evaluate the safety and pharmacokinetics of other antiretroviral agents in pregnant women and neonates, including nevirapine, didanosine (ddI) and stavudine (d4T); studies of protease inhibitors are under consideration. These trials will provide data on the appropriate drug dose and

safety needed for the conduct of future perinatal transmission trials using these agents. Additionally, we are evaluating whether administration of AZT orally during labor will be tolerated by the woman and produce drug levels similar to that with the more complicated intravenous administration used in ACTG 076.

The NICHD/NIAID pediatric trials group also has a protocol that is following infants from ACTG 076 through age 21 years to evaluate if there are any long-term adverse effects of the AZT regimen on uninfected children. Another protocol is following the women enrolled in ACTG 076 for three years postpartum to evaluate any adverse consequences of the regimen for women.

NICHD is in the process of organizing a collaborative retrospective analysis to assess whether cesarean section is associated with decreased transmission compared to vaginal delivery. It involves investigators from a number of studies funded by NIH and CDC as well as several large international studies.

Finally, NICHD is also funding several international trials that will assess different modalities to prevent transmission of HIV from mother to child. A trial comparing a shortened AZT regimen to the ACTG 076 AZT regimen is underway in Thailand. Additionally, following preliminary information from a study in Malawi that indicated that vitamin A deficiency may be associated with increased mother-child HIV transmission, NICHD is funding two studies in Africa regarding the effect that vitamin A supplementation of infected pregnant women will have on perinatal transmission.

Mr. Stokes: I understand that individuals with HIV-2 appear to have some protective mechanism against becoming infected with HIV-1. How close are we to understanding and unraveling this critical difference between the two forms of HIV? What major work is underway here in the U.S. to study these differences?

Dr. Alexander: The ability of infection with HIV-2 to protect against HIV-1 infection is controversial. Some of the currently available data do not support a protective effect of HIV-2 infection against HIV-1 infection.

Overall, there is only approximately 50% similarity between the genes of HIV-1 and HIV-2: the genes responsible for the inside "core" proteins of the two viruses are more alike (60% similarity) than those genes that are responsible for the formation of the outside "coat" or envelope of the two viruses (only 40% similarity). Much of the initial immune response against viruses is directed toward the proteins on the outside envelope of the virus. This means that although there are similarities, the immune response to HIV-2 may differ sufficiently from the response against HIV-1 that protection may not be seen.

This is illustrated by the fact that individuals infected with both HIV-1 and HIV-2 have been identified. In a study of children born to pregnant women from the Ivory Coast in Africa with dual infection, HIV-1 appeared to be more easily transmitted from

mother to child than did HIV-2. Of the infants born to mothers who had infection with both HIV-1 and HIV-2, 24.7% of their infants acquired infection with HIV-1 compared to only 1.2% of their infants acquiring infection with HIV-2. The rate of mother to child transmission for HIV-1 infection from the mothers in this study was similar to that observed elsewhere (about 25%), implying that HIV-2 infection did not appear protective against mother-to-child transmission of HIV-1.

Similarly, in areas (particularly West Africa) where infection with HIV-1 and HIV-2 is found in the same geographic location, heterosexual spread of HIV-2 appears significantly slower than that of HIV-1, consistent with differences in the infectivity of the two viruses. However, these data are not consistent with a protective effect of HIV-2 against HIV-1 infection, as HIV-1 infection appears to be increasing in these geographic areas while HIV-2 infection appears to be diminishing somewhat.

Although HIV-2 infection can be associated with immunodeficiency and the development of an AIDS syndrome, progression to advanced disease appears less common than observed with HIV-1 infection. HIV-2 appears to have less toxicity to immune cells (CD4+ cells) than does HIV-1, and may have lower rates of viral replication and/or a reduced ability to mutate and escape the immune response than does HIV-1. Therefore, the difference in mother-to-child and heterosexual transmission between the two viruses is likely due to a lower viral load and more effective immune response to the HIV-2 virus and higher viral load and less effective immune response to the HIV-1 virus.

A number of basic science and epidemiologic studies (primarily in West Africa) of HIV-1 and HIV-2 infection are supported by the National Institutes of Health as well as by the Centers for Disease Control and Prevention to further elucidate differences between the two viral infections.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are underway at the Institute, and specifically, what can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Alexander: The NICHD supports a large portfolio of human clinical, including *clinical trial*, research. The key areas in which we conduct clinical trials are critical to improving public health and include such topics as:

- ◆ Pediatric and perinatal AIDS, including biomedical and behavioral treatments and interventions to help prevent infection and disease progression
- ◆ Ways to improve pregnancy outcomes, as well as prevent premature births, birth defects, and such conditions as mental retardation. This includes trials to

improve such things as the treatment of infections and other adverse maternal health conditions during pregnancy and the basis of care and advice given to pregnant women regarding nutrition, exercise, stress, and other biological and environmental concerns.

- ◆ New and improved vaccines for childhood diseases
- ◆ Nutrition and its impact on infant, childhood, and adolescent development
- ◆ Pediatric pharmacology
- ◆ Reading and learning disabilities in children
- ◆ New and improved rehabilitation treatments for children and adults, through studies supported by the Institute's new National Center for Medical Rehabilitation Research
- ◆ New and improved contraceptive methods
- ◆ New and improved treatments for infertility

Over the past year, NICHD support has allowed considerable progress in several clinical trial research areas. Some of the most significant advances include:

Premature Births and Maternal Infection: A recently completed clinical trial has determined that the administration of antibiotics to pregnant women whose membranes have ruptured prematurely (between 24 and 32 weeks gestation) reduces the risk of neonatal morbidity and mortality. In this randomized, placebo-controlled, double-masked trial of over 600 infants, the risk of neonatal mortality and morbidity, including respiratory distress and necrotizing enterocolitis was reduced considerably compared with placebo. These results should be useful in reducing the current clinical controversy about administering antibiotics to mothers with premature rupture of the membranes.

Reducing Disease Progression in HIV-Infected Children: Final results of the AIDS Clinical Trials Group (ACTG) protocol 152 are now available. This trial evaluated what drug regimen would be most effective as initial therapy for symptomatic HIV-infected children. It compared the use of zidovudine (AZT) therapy alone, didanosine (ddI) therapy alone, and combination AZT and ddI therapy. Last year, preliminary results indicated that initial therapy with AZT was less effective than the other two regimens. Results this year confirmed this finding, showing that both ddI alone and combination therapy with AZT/ddI were significantly more effective in reducing disease progression in infected children than AZT alone.

Otitis Media and Language Development in Children: NICHD-supported researchers are evaluating the effects of chronic middle ear infection (otitis media or OM) on the cognitive and language development of children who have this common condition. While previous studies have been inconclusive and contradictory, preliminary findings from the current clinical trial of one to two-year olds indicate that there is no meaningful association between parent-reported children's language development and the children's cumulative duration of OM during the first and second year of life. These investigators also found no relationship between parent-child stress and the extent of middle ear effusion in these age groups. Furthermore, researchers determined that OM is somewhat more prevalent in the first year of life than previously thought, particularly in children from lower socioeconomic status.

Mr. Stokes: How much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Alexander: The FY 1997 estimate for clinical trials, including AIDS pediatric trials, is \$76,000,000. This compares to \$77,500,000 in FY 1996, \$73,384,000 in FY 1995, and \$70,513,000 in FY 1994.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under the purview of your Institute?

Dr. Alexander: The NICHD has increased its efforts under the NIH-wide initiative for Research Supplements for Underrepresented Minorities. These increased efforts include: establishing a formal committee within the Institute to oversee the minority supplement initiative, dedicating additional funds from the Institute's budget for these supplements and aggressively seeking co-funding for support of the program. This increase in programming has resulted in 86 new and continuing minority supplements awarded in FY 1995, an increase of 9 over fiscal year 1994. The NICHD also continues to administer the Extramural Associates (EA) Research Development Awards for the Office of the Director, NIH. This program supports minority scientists/administrators and researchers from HBCUs and small colleges and universities. The Deputy Director, NICHD has been directly involved in the curriculum of this program. To increase the number of African American investigators participating in research in the area of early child care, supplements have been made to existing projects within our Network on the Study of Early Child Care to provide salary support for four minority clinical investigators.

To further enhance the career development of NICHD-supported underrepresented minority scientists, NICHD is planning a workshop to be held on the NIH campus. A conference for the purpose of increasing the awareness among the Hispanic population

of the importance of biomedical research in improving health status and to encourage research investigations was supported by the NICHD this year. Over the past 12 months, NICHD staff, including the new Deputy Director, conducted grantsmanship workshops at a number of universities and organizations with high underrepresented minority enrollments. In addition, the new EEO Officer and the Deputy Director have been attending conferences which have large minority participation and which focus on minority health issues.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway with your Institute and the office of research on minority health? Are there specific projects in your Institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Alexander: The ORMH and NICHD are collaborating on the following research projects: Minority Youth Behavior; Cooperative Perinatal Studies and Interventions; and Hemochromatosis Among Native Africans, a subproject of research on iron metabolism. To date, there are no specific projects within the NICHD that are totally funded by the ORMH.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Alexander: The ORMH and NICHD are collaborating on the projects listed above. All of these collaborative projects are co-funded by the NICHD and ORMH. NICHD and ORMH have established a collaborative relationship to enable sound research endeavors to progress with the support of jointly contributed professional expertise, staffing and financial resources. The parties have collaborated in areas where their research goals overlap. For example, NICHD and ORMH are collaborating on efforts that examine behavioral issues, diseases or conditions that may disproportionately affect minorities; improve our understanding of variations in human growth and development; and that provide support to minority scientists who are researching child and maternal health issues. Collaborative efforts to support minority scientists have been ongoing since the early 1980s through various funding mechanisms that have undergone change over the years. Listed on the following page are the specific projects co-funded by NICHD and ORMH.

Projects Co-Funded by the NICHD and ORMH

<i>Project Title</i>	<i>Period of Performance</i>	<i>Total NICHD Support Through FY 1996</i>	<i>Total ORMH Support Through FY 1996</i>
Minority Youth Behavior	FY 1992 - through 1998	\$189,000 (1.0%)	\$17.6 million (78.6%)
Cooperative Perinatal Studies and Interventions	FY 1992 - through 1997	\$1.5 million (10%)	\$13.3 million (90%)
Hemochromatosis Among Native Africans	FY 1993 - through 1997	\$4.9 million (65.6 %)	\$2.6 million (34.4%)

CHILD DAY CARE

Mr. Hoyer: Like my colleagues, I was interested to see in the Washington Post last week that NICHD has completed a study of day care and found that placing children in day care does not weaken a child's emotional bond to his or her parents unless that bond is already weak. Do these results confirm or refute other studies in the same area? Did the study look at all at questions of day care quality? Would this finding apply across the spectrum of day care settings? What does this mean for parents -- both mothers and fathers -- who need to leave their children in day care while they work?

Dr. Alexander: The NICHD Study of Early Child Care is an ongoing study from which we expect many additional important findings. The recent results which were reported found that non-maternal care does not affect attachment unless the mothers are insensitive to their infants. When mothers are insensitive and care is of poor quality, or care is for more than 10 hours per week, or if the child is experiencing several care arrangements, infants are more likely to be insecurely attached.

Previous research which focused on child care effects without taking into account the effects of family characteristics or maternal characteristics on the security of the attachment bond between infants and their mothers, found that infants who are in child care for more than 20 hours per week are more likely to be insecurely attached to their mothers than infants in less hours of care.

Unlike earlier studies about the effects of child care on attachment, the NICHD Study of Early Child Care investigated the effects of quality of care. Quality of care was studied in great detail over two consecutive two-hour visits to child care settings. Observers focused on the individual care that the infants who participated in the study received, and the quality was defined in terms of the immediate experience of each infant.

The findings apply across a spectrum of child care settings, as the investigators focused on all types of non-maternal care, i.e., father care, grandparent care, non-relative care in the child's home, day care homes, and center care.

One cannot generalize from the findings of the NICHD Study of Early Child Care to attachment beyond 15 months, or to the cognitive development, language development, peer relations, compliance, or health development of the same children. Findings pertaining to these other domains of functioning are now under investigation in this study by the same group of researchers.

Mr. Hoyer: Research has found that often, the period from birth to three years old is a critical one in a child's life. Physical, mental and cognitive development is extremely rapid, and children develop relationships with others that will affect their moral development and ability to relate to other people around them. I am pleased that the Head Start program is moving forward in its Head Start 0-3 initiative. What research is

being done on the formative period of 0-3 by NICHD? How are your findings communicated to parents, Head Start and other child care providers to ensure that we are all providing the best possible environment for children?

Dr. Alexander: For many years now, NICHD has supported research about the perceptual, cognitive, linguistic, social, emotional and health development of infants in the first three years of life and beyond. That normative research has produced the methodology and knowledge that can and should guide research that focuses on Head Start eligible children. The findings have been disseminated in the scientific literature, at scientific conferences and, more recently by the media. In the NICHD Study of Early Child Care, about a third of the sample consists of children whose families' incomes are below a ratio of 1.8 in terms of income to needs. Income to needs ratio of 1.0 or below determines eligibility to Head Start. Income to needs ratio of 1.8 or below determines eligibility for school lunch. This means that NICHD staff and affiliated investigators have an unprecedented opportunity to characterize the family conditions, the child care conditions and the cognitive, linguistic, social, emotional and health developmental attainments of infants who have lived in poverty or in near poverty in the early 1990s. We also are in a unique position to follow up these children's development as they enter Head Start and later continue into first grade. In collaboration with the Administration for Children Youth and Families, the Institute is now engaged in a series of studies of the Head Start eligible children who participate in the NICHD Study of Early Child Care. On June 22, 1996 we present our initial findings at the Head Start Third National Research Conference. Our plans for future research include studies of developmental processes in children who grow in poverty and will focus on factors that lead to resilience and success and which may be useful for planning improved intervention programs.

AIDS

Mr. Hoyer: One of the most frightening prospects accompanying the increased heterosexual transmission of AIDS in this country is the accompanying rise in the number of babies born with HIV. What is NICHD doing to respond to this demographic trend? In addition to the positive findings regarding AZT and the maternal transmission of HIV to children, what other approaches are we exploring?

Dr. Alexander: With regard to your first question, NICHD is continuing in its unswerving commitment to the mothers and children most affected by this epidemic. On the heels of the success of ACTG 076, we continue our support of the study (ACTG 185) which will be applicable to the question of how best to treat HIV-infected pregnant women who will not benefit from ACTG 076. We are continuing to explore the needed behavioral studies of social networks and how reproductive choices are made with regard to infectious and similar consequences. We are looking at a number of different modalities to prevent transmission of HIV from mother to child including the use of hyperimmune globulin in addition to AZT, and plan to add protease inhibitors to the prevention regimen. We are also studying use of vitamin A to reduce transmission. We

are, of course, continuing with NIAID to explore how female-controlled methods of contraception may be used to protect women from infectious problems, including HIV. It is our belief that the first response to controlling AIDS in children is to prevent HIV infections in women.

CHILDHOOD ASTHMA

Mr. Hoyer: I am concerned by the rise in childhood asthma, and by the fact that despite the best efforts of researchers in this area we seem to be no closer to identifying a cause or a cure for this disease. Could you update me on research in this area? What promising areas are being explored?

Dr. Alexander: The following response was prepared by NIAID as they are the lead Institute in the area of childhood asthma. The morbidity from childhood asthma continues to rise in the United States. Several lines of research are attempting to find a cure or a better treatment for asthma. Basic studies have shown that asthma is an inflammatory disease, and have identified several new molecules that cause inflammation. Further research is now attempting to produce better and safer medications that block inflammation. Other research is being done to understand the genetics of asthma. A clearer understanding of the genetics of asthma will allow doctors to identify individuals at high risk for developing asthma. We are also seeking to identify the genes that cause asthma and develop new treatments for asthma that block the effects of the asthma-causing genes. Finally, we are focusing research on ways to better use existing asthma treatments, especially among inner city children, who have more severe asthma than children from suburban areas. For example, the National Cooperative Inner City Asthma Study is a project that has devised an intervention program in seven cities to reduce the severity of asthma among inner city children. Preliminary results from this intervention suggest that we can avoid a significant portion of sickness from asthma in these children with proper care.

OTITIS MEDIA

Mr. Hoyer: I am also concerned by the rise in drug-resistant ear infections in young children, which can result in hearing loss, loss of days in school, and great distress for the child and family alike. Has the incidence of otitis media increased, or has it just become more difficult to treat? What is contributing to this problem, and what can we do to address it?

Dr. Alexander: The NICHD, too, is concerned by the rise in antibiotic-resistant otitis media and is funding a large multicenter study of otitis media and its optimal treatment. If treated incorrectly, antibiotic-resistant otitis media may lead to mastoiditis, epidural abscess, brain abscess, and deafness.

Otitis media is the most common infection in infants, affecting as many as 48% of urban children by their seventh month. The incidence of otitis media does not appear to

be increasing. However, the incidence of antibiotic-resistant otitis media has increased rapidly over the past decade. It is estimated that 20-25% of all cases of otitis media now involve antibiotic-resistant bacteria.

The problem stems from the overuse of antibiotics. Most cases of acute otitis media do not require a full ten-day course of antibiotics. Three-to-five days should suffice if there is symptomatic improvement, and there is no need to treat secretory otitis media with antibiotics at all. Even cases of recurrent acute otitis media can be treated prophylactically with one-half of the dose of amoxicillin usually prescribed.

The problem of antibiotic-resistant bacteria is one of global proportions caused by the ubiquitous and incorrect use of antibiotics for viral illnesses and for bacterial infections in the absence of culture and sensitivity testing. The pervasive presence of antibiotics in human and animal hosts acts as a strong and constant selection pressure to promote the survival of antibiotic-resistant bacterial clones. Resistant bacteria develop around the world in an antibiotic-laden environment. Drug-resistant Streptococcus pneumoniae, for example, originated in Africa, then spread to Europe, and more recently to the United States.

The only way to reverse this phenomenon is to reduce the ambient concentration of antibiotics in all human and animal host populations. The solution lies in the re-education of health professionals, consumers, agriculturalists, and veterinarians throughout the world with the assistance of appropriate professional and public health organizations.

RETT SYNDROME

Mr. Hoyer: As you know, I am very interested in Rett Syndrome, a neurological disease which primarily affects young girls. We have heard in these hearings that sometimes discoveries with important implications for a broad spectrum of diseases and conditions are made while studying relatively rare conditions. Will your commitment to Rett Syndrome research continue in 1997? What efforts are in place to encourage young investigators to look at rare disorders, such as Rett Syndrome? How feasible is it for you to fund "high risk" studies where the chance of immediate payoff is less likely? Do you have any plans to involve other Institutes, such as NINDS and NIMH, in your work on Rett Syndrome?

Dr. Alexander: It is a truism in basic research that important discoveries can sometimes be made serendipitously that have implications for a broad spectrum of diseases, including Rett Syndrome, while studying relatively rare conditions. That is the primary reason why NICHD continues to promote basic research in genetics and neurobiology that could ultimately contribute to our understanding of developmental processes and disorders that affect young children.

Our commitment in Rett Syndrome research will continue in 1997. Some progress has been made in understanding the neuropathology of this disorder, suggesting that it results from abnormal regulations of connections in certain brain regions. NICHD has recently published an RFA (request for grant applications) soliciting submission of program project grant applications on autism. Knowledge gained through this grant solicitation could shed light on our basic understanding and potential management of the autistic-like behaviors that are commonly observed in girls with Rett Syndrome. In order to foster research collaborations and to encourage new investigations in the study of Rett Syndrome, NICHD has supported international research meetings and two large program projects. NICHD is also making available Rett patient material through its Brain and Tissue Banks for Neurological Disorders. Research on brain and nervous system development has been targeted by NICHD as a high priority area. Thus, applications from new investigators that relate to Rett Syndrome, as well as those that are deemed as high-risk/high payoff are encouraged.

The NICHD has also implemented a small grants program to support applications from new investigators for pilot projects, feasibility studies, and high risk/high impact research proposals in developmental disabilities. The NICHD is co-sponsoring, with the Office of Rare Diseases, Office of the Director, NIH, two workshops to stimulate research in rare diseases and these workshops will target participation from new investigators.

SUDDEN INFANT DEATH SYNDROME

Mr. Hoyer: We have heard of the Institute's exciting success with the "Back to Sleep" campaign, and I know this involved getting parents, in most cases to do things differently than their parents did in regard to their babies' sleep position. How have you gone about significantly changing the behavior of these new parents?

Dr. Alexander: We are bringing about this change by continuing to get the message out that healthy babies should be placed on their back or side to sleep. The success of this campaign is dependent on this change in sleep position becoming standard practice for parents. Parents, however, are not the only audience to reach to bring about this change. We must also educate doctors, nurses, and other health professionals, as well as those responsible for the day to day care of infants such as grandparents, day care workers, and babysitters.

BIRTH DEFECTS

Mr. Hoyer: We learned with great interest of NICHD's success in overcoming the genetic metabolic error responsible for many cases of neural tube defects, such as spina bifida. Can such a serious problem be eliminated by just supplementing a pregnant woman's diet with folic acid?

Dr. Alexander: We estimate that approximately 50 percent of neural tube defects can be prevented by folic acid supplements. Unfortunately, these defects occur very early in pregnancy, within the first 28 days after conception, when many women are not even aware that they are pregnant. Therefore, it is necessary to increase women's folic acid intake before they become pregnant. The U.S.P.H.S. has recommended that all women of childbearing age take a tablet containing 0.4mg of folic acid each day; however, a survey conducted by the Centers for Disease Control and Prevention has shown that this recommendation is not widely followed. The U.S.F.D.A. has recently issued regulations requiring that grain products be fortified with folic acid. This should increase the folic acid intake in almost all women. Further research is being planned to determine whether this approach will produce the maximum protective effect.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

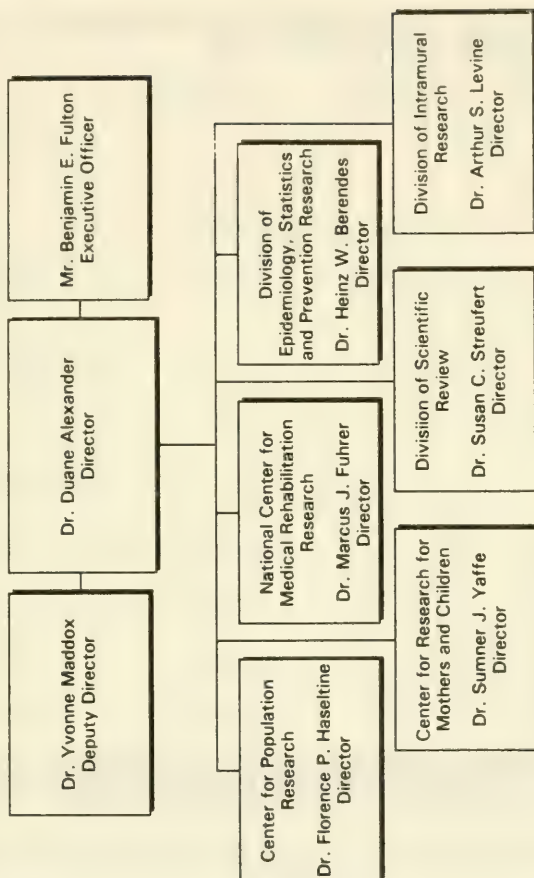
NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

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NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development



NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

For carrying out Section 301 and title IV of the Public Health Service Act with respect to child health and human development, \$543,441,000.

Note—A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91 P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Amounts Available for Obligation 1/

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Appropriation.....	\$513,409,000	\$595,162,000	\$543,441,000
Reduction in accordance with PL 103-333.....	-557,000		
Resission in accordance with PL 104-19.....	-687,000		
Subtotal, Adjusted Appropriation.....	512,165,000	595,162,000	543,441,000
Real transfer to Other NIH Institutes through the NIH Director's one percent transfer authority.....	-438,000		
Comparative transfer to:			
Office of AIDS Research, NIH for HIV activities.....		-60,713,000	
Other NIH Institutes for Management Fund adjustment.	-2,696,000		
Subtotal, adjusted budget authority.....	509,031,000	534,449,000	543,441,000
Unobligated balance, lapsing.....	-85,000		
Total obligations.....	508,946,000	534,449,000	543,441,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1995--\$25,573,000; FY 1996--\$25,573,000; FY 1997--\$25,573,000.

Also excludes funding for HIV/AIDS activities: FY 1995--\$58,667,000; FY 1997--\$60,209,000, included in the Office of AIDS Research, NIH.

Note: Excludes \$85,000 in FY 1995 and \$109,000 in FY 1996 for royalties.

Justification

National Institute of Child Health and Human Development

FY 1995		FY 1996		FY 1997		Increase or Decrease	
Actual		Appropriation		Estimate			
FTE	BA	FTE	BA	FTE	BA	FTE	BA
486	\$509,031,000	483	\$534,449,000	483	\$543,441,000	--	\$+8,992,000

General Statement

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute of Child Health and Human Development (NICHD). Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The NICHD uses the full spectrum of research approaches from laboratory sciences through epidemiological and clinical research approaches as it pursues its mission and is the lead agency within the NIH for research on maternal and child health, as well as on the population sciences, and medical rehabilitation.

Highlights of the year for the National Institute of Child Health and Human Development include the award of the Nobel Prize to two grantees for research relevant to birth defects, and a major reduction in infant mortality in the United States that has come as a direct result of the NICHD research activities.

In October 1995, it was announced that the Nobel Prize for Physiology or Medicine was awarded to three scientists, two of whom, Dr. Edward B. Lewis of the California Institute of Technology and Dr. Eric Wieschaus of Princeton, are long-term grantees of the NICHD. Dr. Lewis has received research support for 21 years and Dr. Wieschaus, who received his first grant from the Institute in 1969, is currently an NICHD Merit Awardee. These extraordinary scientists were honored for research on a group of genes that control embryonic development in *Drosophila*, the fruit fly. *Drosophila* may seem very distant from human biology, but it provides scientists with a model for early human development. In both cases, the fertilized egg changes from two symmetrical cells into a very widely differentiated and complex organism. This Nobel-prize-winning research makes a major contribution to the understanding of birth defects.

Intrigued by observations of a fly with an extra pair of wings, Dr. Lewis, in the 1970s began his prize-winning work. He and Dr. Christiane Nusslein-Volhard, a German scientist and the third Nobel awardee, used a new approach to expose systematically the fruit flies to toxic substances to cause genetic defects, and gradually isolated the critical gene controlling body part formation. Then Dr. Wieschaus and Dr. Nusslein-Volhard continued and expanded the work. Related

research on birth defects, using *Drosophila* and other animal models, continues in the NICHD's own labs and with grantees around the country.

A major impetus for the establishment of the NICHD by Congress in 1962 was the high infant mortality rate in the United States. In 1994, that rate dropped 4 percent from the previous year to an all-time low of 7.9 per thousand live births. This represents a decline of 69 percent, from 25.3, since the NICHD began, one of the greatest improvements in any of our public health measures. NICHD research has played a major role in this decline. The decline from 1993 to 1994 is illustrative, as the decline was due almost entirely to reduced deaths from Respiratory Distress Syndrome (RDS) and Sudden Infant Death Syndrome (SIDS).

For women with high risk pregnancies, corticosteroid treatments reduce the risk of early labor and reduce deaths from RDS. The increased use of antenatal corticosteroid in at-risk pregnancies to prevent RDS and endocranial hemorrhage was demonstrated to be effective by NICHD research and brought to more extensive clinical use as a result of an NICHD Consensus Development Conference. For premature newborns, the administration of surfactant aids normal lung development. The development of surfactant, a complex natural substance, was a direct outgrowth of research supported by the NICHD and the National Heart, Lung and Blood Institute.

The decline in infant mortality due to reductions in Sudden Infant Death Syndrome (SIDS) was a direct result of NICHD research. A national public education campaign, "Back to Sleep," is advising parents to place their babies on their back or side to sleep and, at the same time, research is leading to an understanding of the underlying causes of SIDS. Recent studies have shown a reduced number of neurons in a specific center in the brain responsible for reaction to dangerously high levels of carbon dioxide or decreased oxygen levels. Normally a baby would receive cues from this brain center and would shift position to gain more oxygen, but some babies do not receive the right signals. Another study showed that babies who later died of SIDS had less flexible and responsive breathing patterns. Such studies are leading to identification of infants at high risk for SIDS and to ways to monitor sleeping patterns.

The "Back to Sleep" campaign is a direct result of the NICHD research showing a clear link between infant sleep position and SIDS. This public information campaign has changed practice from 80 percent of infants sleeping on their stomachs to 70 percent sleeping on their back or sides, the recommended positions. Preliminary data for 1995 suggest a further reduction in SIDS deaths. This year, NICHD will intensify and broaden the "Back to Sleep" campaign to reach fathers and grandfathers.

Despite the improvements, our infant mortality rate remains too high. High rates of premature birth and consequent low birth weight take a tragic toll and carry an economic burden, beginning with neonatal intensive care in the hospital and often extending through childhood. Premature birth and low birth weight increase the risk for infant mortality and mental retardation, cerebral palsy and other problems. Rates vary among population groups. In 1993, the rate of low birth weight among African Americans was 13.3 percent compared to 6.2 percent among

Hispanics and 6.2 percent among white Americans. The NICHD supports a Newborn Intensive Care Network with clinical trials to find effective therapies for very tiny premature infants.

Prevention of premature delivery is an important goal. Although many factors contribute to premature delivery, NICHD research has shown that a common vaginal condition known as bacterial vaginosis significantly increases a woman's risk of the premature delivery, perhaps accounting for 20 to 40 percent of cases. Although bacterial vaginosis is easily diagnosed through a laboratory test, women may be personally unaware of the infection. This new research also shows that treatment of bacterial vaginosis with certain antibiotics can reduce the risk of a premature delivery. Studies continue to determine the most effective treatment for this and other vaginal infections.

All parents hope that their babies will be healthy, but in addition to the 32,000 infants who die before age one, many are disabled by birth defects. This year, NICHD scientists described genetic abnormalities which explain why folic acid may prevent neural tube defects (spina bifida, anencephaly, and other serious brain and spinal cord disorders). This is an important advance, raising the possibility of identifying women at high risk who would specifically benefit from folate supplementation before pregnancy. NICHD research helped to lay the groundwork for the recent Food and Drug Administration decision to fortify foods with folic acid in order to make it more likely that women would have sufficient amounts before and immediately after becoming pregnant.

Brain injuries can occur throughout life. More than one million people incur traumatic brain injury (TBI) or stroke each year. A majority of these people survive, but have neurological damage leading to motor or cognitive defects. Research supported by the NICHD is exploring biochemical, physiological, and behavioral strategies to prevent such disabilities, to reduce their severity, or to enhance the success of rehabilitation efforts. Death of nerve cells is a significant cause of disability after such an injury. Animal studies have shown that a gene therapy intervention is successful in maintaining greater numbers of neuronal connections, thus enhancing the potential to continue functioning.

Research on contraceptive drugs and devices, on the effects of postmenopausal hormone use and fertility drugs, and on barrier contraceptives (including microbicial spermicides) has major implications not only for prevention of unplanned pregnancies, but also for the prevention of transmission of disease and to stem some health problems of advancing age.

Contraceptives that reduce the spread of sexually transmitted diseases (STD), including AIDS, can have a major impact on public health. NICHD-supported studies are evaluating microbicial products to be used vaginally, including a new spermicide that kills bacteria and viruses.

Purpose and Method of Operation

The NICHD research is carried out by five administrative entities: the Center for Population Research (CPR); the Center for Research for Mothers and Children (CRMC); the National

Center for Medical Rehabilitation Research (NCMRR); the Division of Epidemiology, Statistics and Prevention Research (DESPR); and the Division of Intramural Research (DIR). The NICHD carries out its extramural programs in the first three entities through support of research project grants, center grants, other research grants, training grants and fellowships, and research and development contracts. In addition, the Institute supports an intramural research program that includes prevention research. The scientific and administrative management of the Institute is funded through the research management and support budget mechanism.

Overall Budget Policy

The FY 1997 budget request for the NICHD totals \$543,441,000. This represents an increase of \$8,992,000, or 1.7 percent, over the FY 1996 estimate. The FY 1997 request will support 483 full time equivalent positions (FTEs), the same number as the FY 1996 estimate. Total funding and FTE levels for the NICHD during the last five years has been as follows:

	<u>Amount</u>	<u>FTEs</u>
FY 1992	\$484,022,000	577
FY 1993	\$488,960,000	562
FY 1994	\$495,719,000	504
FY 1995	\$509,031,000	486
FY 1996	\$534,449,000	483

Of the increase requested in FY 1997, \$4,000,000 is targeted towards special areas of emphasis to highlight NIH initiatives. The NIH areas of emphasis and the corresponding targeted increases include: biology of brain disorder - + \$1,000,000, new approaches to pathogenesis - + \$1,000,000, new prevention strategies against disease areas - + \$2,000,000.

The NICHD FY 1997 budget request for research project grants is \$305,918,000. This is an increase of \$10,016,000 or 3.4 percent over the FY 1996 level. Of the increase provided, \$4,000,000 is targeted for the NIH emphasis areas described above. In the FY 1997 request, NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to decline to 2.2 percent as measured by the Gross Domestic Product Implicit Price Deflator and to 3.7 percent as measured by the Biomedical Research and Development Price Index. Thus, in FY 1997 noncompeting RPGs would receive direct cost increases over FY 1996 of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities. The FY 1997 request will support 1,259 total RPGs including 299 competing awards. This is an increase of 8 total and 9 competing awards over the FY 1996 estimate.

In research centers, a total of \$46,577,000 is requested for FY 1997. This represents the same number of centers and the same dollar level as the FY 1996 estimate.

Funding for activities in the other research mechanism which includes research career awards, cooperative clinical research, minority biomedical research support and other research grants would be supported for a total of \$33,051,000. This also reflects approximately the same dollar level as the FY 1996 estimate.

The request for R&D contracts is \$40,895,000, a decrease \$1,331,000 or 3.1 percent from the FY 1996 level.

In research training, the Institute will support 747 full-time equivalent trainees in FY 1997 for \$18,981,000. This is the same number of trainees and \$307,000 over the FY 1996 estimate. The additional funds will provide research trainees with a 2.2 percent stipend increase. This is the first increase in stipend levels since FY 1994.

In intramural research and research management and support, FY 1997 funding levels are \$73,725,000 and \$24,294,000, respectively. These are the same dollar levels as included in the FY 1996 estimate.

Extramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1997

Authorization: Indefinite.

Budget Authority:

<u>FY 1995</u>	<u>FY 1996</u>	<u>FY 1997</u>	<u>Increase</u>
<u>Actual</u>	<u>Estimate</u>	<u>Estimate</u>	<u>or</u>
			<u>Decrease</u>
\$412,824,000	\$436,430,000	\$445,422,000	+\$8,992,000

The extramural research program of the NICHD is comprised of the following budget activities: Population Research, Research for Mothers and Children, and Medical Rehabilitation Research.

Funding for the NICHD extramural research program during the past five years has been as follows:

	<u>Amount</u>
FY 1992	\$391,018,000
FY 1993	394,118,000
FY 1994	400,023,000
FY 1995	412,824,000
FY 1996	436,430,000

Rationale for the Budget Request

The FY 1997 request for the NICHD extramural program is \$445,422,000, an increase of \$8,992,000 over the FY 1996 level. These funds will provide support for the following activities: Population Research, \$142,794,000, an increase of \$1,917,000 or 1.4 percent over the FY 1996 estimate of \$140,877,000; Research for Mothers and Children, \$283,520,000, an increase of \$6,287,000 or 2.3 percent over the FY 1996 estimate of \$277,233,000; and Medical Rehabilitation Research, \$19,108,000, an increase of \$788,000 or 4.3 percent over the FY 1996 estimate of \$18,320,000. Examples of current program activities and future plans are described below.

POPULATION RESEARCH

The Center for Population Research (CPR) at the NICHD leads the primary federal effort in population research. In meeting this responsibility, the CPR develops and supports programs of research and research training in the biomedical, epidemiologic, and demographic and behavioral aspects of the population sciences. Funding is provided for fundamental biomedical research in the reproductive sciences relevant to problems of human fertility and infertility, the development of safe and effective methods for fertility regulation, the evaluation of the benefits and risks of current contraceptive methods and fertility related technologies, and demographic and behavioral sciences research on the causes and consequences of population structure and change.

Demographic and Behavioral Sciences: Research supported by the demographic and behavioral sciences program includes the causes and consequences of out-of-wedlock and teen childbearing, family and household behavior, immigration, infant mortality and other topics relating to the growth and changing characteristics of our nation's most valuable asset, its population.

In response to a directive in the Violent Crime Control and Law Enforcement Act of 1994, NICHD personnel collaborated with top-ranked scientists and other DHHS staff to produce a comprehensive report to Congress on the problem of out-of-wedlock childbearing. Although the dramatic increase in the past 50 years in out-of-wedlock childbearing had slowed slightly during the early 1990s, the still-high levels seriously affect the well-being of children and society. Causes of the trend were identified as including declining economic opportunities for young men and women and changes in attitudes and values concerning marriage and the acceptability of unwed parenthood. Both out-of-wedlock childbearing and fatherhood have been identified as high priority scientific research areas for the NICHD.

More than half the pregnancies in the U.S. are mistimed, unintended, or unwanted, thus contributing to high rates of abortion. The NICHD has launched a set of research projects to examine why, in the face of widespread access to contraception, high rates of unintended pregnancy persist. Related studies have documented that media coverage of some women's concerns with contraceptives like Norplant and Depo-Provera had an immediate and negative impact on the adoption of the methods by new users, but little impact on continuation by women who were already using them.

Contraceptive and Reproductive Evaluation: The NICHD supports research on the medical effects of contraceptive drugs and devices; on the role of noncontraceptive gynecological products or procedures, such as postmenopausal hormones and fertility drugs; and on the role of barrier contraceptives (including spermicides) in disease prevention as well as contraception.

Several studies are examining the effects of oral contraceptives on various aspects of the health of women. The lifetime risk of breast cancer for women who have taken oral contraceptives is being assessed by the NICHD Women's Contraceptive and Reproductive Experiences (CARE) Study, which will recruit approximately 10,000 women from five widely divergent U.S. geographic regions. Women who first used oral contraceptives in the 1960s and

1970s and are presently entering the ages of highest risk of breast cancer will be studied. In addition, other studies are evaluating the relationship between the use of current low-dose oral contraceptives and cardiovascular diseases (stroke, thromboembolism, and myocardial infarction).

The NICHD has expanded its program in evaluating female controlled barrier contraceptives (including spermicides). A clinical trial has been designed and funded to evaluate the protection afforded by the female condom against gonorrhea and chlamydia by comparing user/nonuser infection rates among women relying on the female condom to those relying on the male condom. The NICHD plans separate studies to evaluate the female condom and various spermicides for contraceptive efficacy.

Contraceptive Development. The NICHD's contraceptive development program supports the development of new or improved forms of contraception. The program funds basic and applied research, as well as clinical research on novel methods of contraception, improvements on existing methods, and development and evaluation of new chemical compounds.

The vagina and cervix form a complex ecosystem about which little is known. Recently funded grants will support the study of the changes within the vaginal environment that occur with sexual activity, infection, or the introduction of products designed for vaginal use. Acquiring this knowledge is crucial because irritation and/or changes in vaginal flora may increase a woman's susceptibility to STD infections.

Latex condoms (the only devices proven to prevent STD transmission) are limited in terms of shelf life and user acceptability; and additionally, a significant number of men and women are allergic to latex. Four contract projects have been funded to develop and test non-latex condoms.

Continued testing on new oral active estrogens synthesized via contract-supported projects has identified two promising candidates which are expected to be more potent with fewer side effects than currently used oral estrogens. Also within the last year, the NICHD prepared and filed investigational new drug (IND) applications for testosterone bucyclate and levonorgestrel butanoate. Levonorgestrel butanoate is a long-acting progestin which has potential for both male and female contraception. Testosterone bucyclate, a long-acting androgen, was developed as a replacement androgen for use in male hormonal contraception or in testosterone-deficiency conditions.

The NICHD is establishing a clinical trials network to test promising contraceptives expeditiously and efficiently. In addition, the network will be used to resolve questions about currently used spermicides, including minimum effective dose and duration of efficacy. This information is critical in order to set a standard for new products to equal or surpass; additionally, it will provide a basis for rational use of existing spermicides which may result in less irritation and better user acceptability.

The NICHD Contraceptive Development Research Centers program has made important advances in the areas of vaccine development, androgen implants, and vaginal rings. The vaginal rings project is in the clinical testing stage.

Reproductive Sciences: The NICHD's reproductive sciences program promotes and supports basic and clinical research designed to explore fundamental mechanisms regulating human fertility and to translate such knowledge into clinical applications for the cure or alleviation of infertility, as well as treatment of reproductive disorders to preserve fertility.

Infertility affects 2.4 million married couples in the U.S. with health care costs exceeding \$1 billion annually. Male factor infertility accounts for at least 40 percent of the reported infertility cases in the U.S. New studies conducted this year have revealed that a significant number of infertile men with an absence of sperm in the semen (azoospermia) carry genetic mutations in a small, specific (master gene) region of the DNA in the male Y chromosome that controls the developmental progression of spermatogenesis. This ground-breaking study may provide a wholly new means of diagnosing, providing genetic counseling and optimizing treatment for this form of male infertility.

An inherited disease called congenital lipid hyperplasia (CLH) causes a defective synthesis of all gonadal and adrenal steroid hormones. Surviving genetic males lack testicular testosterone synthesis and are born with external female genitalia. Without androgen steroid hormone replacement therapy, affected individuals die in infancy. In a remarkable break-through study, it has been found that CLH is caused by a defect in a gene that codes for a mitochondrial protein called steroidogenic acute regulatory (STAR) protein which changes cholesterol into the steroid hormones. This work offers promise for developing new clinical treatments for CLH and related diseases.

The Infertility Centers Program, authorized by the NIH Revitalization Act of 1993, has completed several new clinical studies aimed at improving the treatment of infertility. Hypergonadotropic amenorrhea is a condition in which women with premature ovarian failure (POF) infrequently ovulate and rarely achieve a pregnancy. The completion of a randomized, controlled trial of estradiol replacement therapy in such women has shown that such therapy does not improve the rate of folliculogenesis or ovulation. These findings have important implications for planning treatment courses for women with POF. Other clinical studies involving women with arrested ovarian follicular development due to polycystic ovary syndrome (PCOS) have shown that ovarian hyperstimulation treatments with gonadotropins result in hormonal responses within the ovary that are significantly blunted and result in significantly less successful assisted conception outcomes. These findings are leading to new treatment approaches for women with PCOS women.

Endometriosis is a common, distressing and mysterious disease of women that is associated with infertility. It leads to painful, scarring adhesions and dysfunctional effects in pelvic tissue. A new study using a rat model of endometriosis has identified conditions in which treatment with a gonadotropin-releasing hormone analog (GnRH-a) reduces adhesion formation. This finding

suggests improved designs for GnRH-a therapy that may provide a two-pronged attack on endometriosis which both relieves the pain of the present symptoms and prevents infertility.

RESEARCH FOR MOTHERS AND CHILDREN

The Center for Research for Mothers and Children (CRMC), is the primary focus of support for research and research training concerning maternal and child health at the NIH. The entire range of life from conception to maturity is addressed by the CRMC's biomedical and behavioral research programs. These programs are designed to advance the goal of ensuring the birth of healthy babies who have the opportunity to reach adulthood unimpaired by physical or mental disability and, therefore, are able to achieve their full genetic potential. The CRMC has a special interest in programs designed to prevent prematurity, low birth weight and Sudden Infant Death Syndrome (SIDS), conditions which are related to infant deaths in the U.S. Other CRMC research programs have as a goal the prevention or amelioration of birth defects, mental retardation, learning disabilities, pediatric AIDS, childhood injury, and other conditions which impede optimal physical or behavioral development. The CRMC also supports studies of normal physical, cognitive, psychological and social development.

Infant Morbidity and Mortality: The NICHD Maternal-Fetal Medicine Units (MFMU) Network, established in 1986, continues to focus much of its effort on the prevention of preterm birth, because of the persistent problem of low birth weight in the United States, and the disparities which continue between population subgroups in this regard. The MFMU Network recently reported that if the protein fetal fibronectin is present in the lower genital tract of pregnant women, the risk of spontaneous preterm birth is increased 10-20 fold. The test is highly sensitive, in that a positive test at 24 weeks of gestation identifies about 60% of mothers who will deliver before 28 weeks gestation. This association is more powerful than any other predictor, including prior preterm births. Further analysis has shown that the risks of clinical infection of the mother at birth and of the newborn were also elevated in fibronectin-positive women. Based on these results, it is postulated that the presence of fibronectin can reflect a subclinical infection of the fetal membranes. This process may worsen sufficiently to trigger preterm labor. A randomized clinical trial was developed and recently implemented to test whether antibiotic treatment of fibronectin-positive patients can prevent, or delay, preterm labor and birth. If an effective treatment can be found, the potential benefit would be greater for subpopulations, such as African Americans, that have higher prevalence of fibronectin positivity. Thus, appropriate screening and intervention may potentially reduce the current racial differential in very low birth weight, and hence, in infant morbidity and mortality.

Approximately one-third of cases of preterm birth follow spontaneous rupture of the membranes (pPROM). This condition is strongly associated with both maternal and neonatal infectious morbidity. However, despite years of research, clinicians remain intensely divided on the management of pPROM. This year, the MFMU Network completed a randomized clinical trial with pPROM patients between 24 and 32 weeks gestation, using antibiotics vs. placebo. The treatment did prevent infection, delayed birth, and reduced serious illnesses of the newborn, such as respiratory distress, cranial hemorrhage, as well as death.

NICHD, in a collaborative effort with the National Institute of Drug Abuse, the Agency for Children, Youth, and Family and, the Center for Substance Abuse Treatment, is continuing a large interdisciplinary study of the sequelae of intrauterine drug exposure. Over 19,000 women were screened and 1,400 infants enrolled in a 3-year follow-up study to assess acute and long-term development and the life circumstances of these infants and their families, including services needed, quality of parenting, ongoing drug exposure, the role of violence, and lead exposure. A special neurodevelopmental battery will assess subtle cognitive, social, and language developmental disabilities. Of special interest is the unique data set on caretakers, child protective service referrals, foster and congregate care placement, services provided to infants and their caretakers, household stability, etc. The findings will lead to interventions to improve the developmental outcome of these infants.

Genetic Basis of Hirschsprung's Disease: Major breakthroughs have been made in elucidating the genetic basis of Hirschsprung's Disease (HSCR; also called aganglionic megacolon), a congenital disease that occurs in 1 of 5,000 live births and results in a colon that lacks innervation. The consequence is intestinal blockage, usually chronic severe constipation that presents in the neonatal period and requires surgical correction. Recent studies identified several genes that are responsible for HSCR. The first HSCR-related gene to be discovered, HSCR1, accounts for only about 10% of Hirschsprung's cases. Subsequent studies revealed a more prevalent defect in the gene (HSCR2) coding for the endothelin-B receptor that impairs the receptor's ability to respond to its ligand. Homozygotes for this mutation have a 74% chance of developing HSCR. Furthermore, alteration of the endothelin-B receptor gene by targeted disruption in mice produces megacolon. Thus, the endothelin receptor appears to be involved in a previously unknown pathway that controls the innervation of the digestive tract.

NICHD Initiative on Primary Immunodeficiencies: The NICHD has developed a partnership with the Jeffrey Modell Foundation (JMF) to initiate and implement a program in 1996 that supports research on primary immunodeficiencies and raises public awareness of these devastating conditions. The goal of this research initiative is to elucidate the molecular and genetic mechanisms responsible for normal and defective development of the immune system in order to develop efficacious diagnostic, therapeutic and prevention strategies for primary immunodeficiencies. Primary immunodeficiency diseases result from congenital genetic defects causing abnormal development of the immune system. These inherited diseases are manifested mostly during infancy and early childhood and vary in symptomatology and frequency. Severe conditions, such as severe combined immunodeficiency, or "Bubble Boy Disease," [1 of every 10,000 to 100,000 live births] normally result in death within two years of life unless treated successfully with either expensive bone marrow transplantation, enzyme replacement or gene therapies. Milder forms, such as selective immunoglobulin A deficiency [1 in 500 individuals] result in susceptibility to numerous chronic infections usually requiring long term immunoglobulin treatment or hospitalization.

Osteoporosis Prevention: A longitudinal study on calcium supplementation and bone accretion has shown that supplementing the diets of the girls from ages 14-16 produced more than twice the increment in bone density as supplementing them from ages 12-14 indicating that a specific two-year window of opportunity may exist during which calcium supplements maximize

bone acquisition during adolescence. Although it is known that calcium in milk and other dairy products build strong bones, weight-conscious teenage girls are reluctant to partake in the consumption of dairy products. The average teenage girl consumes only about 700 milligrams of calcium per day, which is 500 milligrams less than the recommended daily allowance.

Lipid Profiles of Children on a High-Fat Diet: A certain serum lipid profile in adults has been identified as a risk factor for premature coronary artery disease. This profile may be generated or exaggerated by diets comprising more than 30 percent of calories from fat. Reduction of the amount of fat in the diets leads to a reduction in the frequency of heart attacks and chronic symptomatic coronary artery disease. It is not clear if the relationship between diet and lipid levels observed in adults also applies in children. The Institute plans to support a study to measure the lipid profile in serum samples obtained from children before, during, and after treatment with the ketogenic, high fat, diet. This diet is used for the treatment of intractable epilepsy. About one-half of the children respond to the treatment and are maintained on the high fat diets for two years or longer. These studies should allow a calculation of a correlation between diet and the risk-associated lipid profile and be useful in planning for future tracking studies of dietary modification in children with familial premature coronary artery disease.

Learning Disabilities: During the past five years, NICHD-supported scientists have obtained data that uncovers the core cognitive, genetic, and neurobiological deficits in reading disability (RD), the most prevalent form of learning disabilities (LD). Specifically, cognitive scientists and neuroscientists at the NICHD Learning Disability Research Centers (LDRCs) have found and reported that RD represents a disorder of language, and more specifically an impairment in phonological processing ability.

NICHD Study of Early Child Care: NICHD supports studies from 10 participating sites on the effects of early child care on social, emotional and cognitive development of children from birth to three years of life. The aim is to determine how non-parental care (quality and extent of its use) interacts with characteristics of the children, their family and home to influence children's development. Preliminary data indicate that the decision to place an infant in a child care setting depends on family economics, particularly the employment of the mother. Infants who entered care earlier than others came from families who depended more heavily on maternal incomes and whose mothers believed that maternal employment has positive effects on child development. Families who use more hours of child care had mothers with less education, who worked longer hours.

Rett Syndrome: Rett syndrome is a neurological disorder that seems to occur only in females. It has an estimated frequency of 1/15,000 births. Development appears normal for the first few months of life, then a period of stagnation or even regression occurs, resulting in moderate to severe neurological problems including seizures, lack of mobility, abnormal hand movements, and autistic-like behavior. NICHD has supported international research meetings on Rett, two large program projects, and other research activities related to this syndrome. NICHD is also making available Rett patient material through its Brain and Tissue Banks for Neurodevelopmental Disorders. Most occurrences of Rett appear to be sporadic, but some cases suggest a genetic component. Some important research is focusing on this aspect along with the

support of Rett families and research registries. Some progress has been made in understanding the neuropathology of this disorder, suggesting that it results from abnormal regulation of connections in certain brain regions. Thus, Rett is now conceived as a defect in early development rather than a neurodegenerative disorder. Neuropathology and brain imaging, as well as related studies in animal models, suggest that certain neurotransmitter pathways may be affected which could suggest potential pharmacological interventions. Nutritional studies continue to show that high-energy, high-protein supplements result in improved growth and metabolism in affected girls.

Autism: Autism is a developmental disability that is evidenced in the infancy and toddler periods; it results in severe impairment in communication, social interaction, and the ability to live and work in the community. For the first time, with NIH support, standard diagnostic criteria have been identified for the autism spectrum disorders and incorporated into both the U.S. (DSM-IV) and international (ICD-10) classification systems. The NIH sponsored three special activities to address this pressing public health problem: (1) An NIH Autism State-of-the-Science conference and a report of the findings and recommendations is being published. (2) Highlights of the report were presented to more than 1600 parents and professionals in inter-institute seminars at the national conferences of the Autism Society of America in Greensboro, North Carolina, and the Autism National Committee in Arlington, Virginia. (3) Additional presentations are scheduled at parent/professional conferences, national workshops for clinicians, and national conferences for parents.

MEDICAL REHABILITATION RESEARCH

The mission of the National Center for Medical Rehabilitation Research (NCMRR) is to develop the scientific knowledge needed to promote the health, productivity, independence, and quality of life of people with physical disabilities. The Center brings these issues to the attention of America's best scientists in order to capitalize upon the myriad advances occurring in the biological, behavioral, and engineering sciences. NCMRR provides funds for research and research training, facilitates the coordination of relevant research within NIH and other agencies, and disseminates information to scientists, rehabilitation service providers, and to persons with disabilities and their families.

Rehabilitation of Persons with Brain Dysfunctions due to Stroke or Traumatic Brain Injury: A behaviorally oriented investigation being supported by NCMRR focuses upon people with moderately severe to quite severe injury of the brain due to accidents or strokes. Studies will identify characteristics of the injury and the associated cognitive changes that, on a predictive basis, distinguish people who will have substantial long-term difficulties in their cognitive functioning and relations with other people from those who will have little or no difficulty. The findings are expected to be useful in allocating health services, improving and evaluating their effectiveness.

Assistive Technologies: In 1990, more than 13 million Americans with physical impairments used assistive technology to improve their functioning in activities of everyday life and to reduce their dependency on assistance by other people. Drawing upon advances in computer science,

communication technology, engineering, and biomaterials technology, an array of projects is aimed at developing a new generation of assistive technology of unprecedented effectiveness, durability, safety, and affordability. For instance, a series of projects will provide users of a prosthetic arm or leg with a sense of touch and the ability to distinguish hot from cold. Other projects are being devoted to developing advanced forms of wheeled mobility, improved means of enhancing limb movement and bowel and bladder control, and more effective ways of controlling the environment at home or work.

Women with Disabilities: More than 20 million women in the United States have a physical disability that limits their ability to perform activities of daily living. Little is known about the impact of disability on the sexuality of these women and about the consequences for their quality of life. An ongoing NICHD-supported study is providing information about how women with physical disabilities view their own sexuality, their success in establishing successful personal relationships, and their experience in obtaining disability related health care. The results to date indicate that women with disabilities, particularly those with early onset disabilities, enter into intimate relationships much later than other women and receive much more limited information regarding their reproductive options, including access to contraceptive information and to gynecological care. Furthermore, this study reports that women with disabilities of all ages experience a much higher level of abuse than was anticipated, indicating a need for research to identify interventions to prevent such abuse. Research is also needed to identify strategies to improve the fitness and well being of women with various degrees of impaired mobility. Strategies will be encouraged that incorporate appropriate exercise paradigms to promote cardiovascular fitness, prevent further disability by overuse injuries or osteoporosis, or that promote a healthy lifestyle through adequate nutrition and stress reduction.

Intramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1997
 Authorization: Indefinite.

FY 1995		FY 1996		FY 1997		Increase or Decrease	
<u>Actual</u>		<u>Estimate</u>		<u>Estimate</u>			
<u>FTE</u>	<u>BA</u>	<u>FTE</u>	<u>BA</u>	<u>FTE</u>	<u>BA</u>	<u>FTE</u>	<u>BA</u>
303	\$70,059,000	303	\$73,725,000	303	\$73,725,000	--	---

The NICHD Intramural Research Program is comprised of the Division of Intramural Research and the Division of Epidemiology, Statistics and Prevention Research. The Division of Intramural Research conducts laboratory and clinical research on reproduction and on the biomedical and behavioral aspects of human development. The Division of Epidemiology, Statistics and Prevention Research conducts field studies of determinants of infant mortality and morbidity and interventions to promote health and well being in mothers and children.

Funding for intramural research during the past five years has been as follows:

	<u>Amount</u>	<u>FTEs</u>
FY 1992	\$66,401,000	370
FY 1993	69,628,000	363
FY 1994	69,693,000	316
FY 1995	70,059,000	303
FY 1996	73,725,000	303

Rationale for the Budget Request

The FY 1997 request for intramural research is \$73,725,000, the same amount as the FY 1996 estimate. The following are examples of current activities and future plans.

LABORATORY AND CLINICAL RESEARCH

Scientists in the Division of Intramural Research will continue to pursue promising leads concerned with the biological and neurobiological, medical, and behavioral aspects of normal and abnormal human development. The key to the prevention of common "adult" diseases, such as cancer, heart disease, mental illness, immunologic disorders, and premature aging, lies in an understanding of the rules which govern early development. Research is carried out in patients as well as in a diversity of animal models. Currently, two themes of basic investigation are being emphasized throughout the program: the structure, function, and transmission of genes --to the development of gene therapy; and signal transduction, the complex pathway by which

environmental stimuli induce a signal at the cell surface which eventuates in the expression of genes in the nucleus. The NICHD also supports an intensive effort in vaccine development, seeking to prevent the common but serious bacterial infections of children, but also to look toward the rapidly appearing day when antibiotics fail in many diseases and prevention strategies are needed. There is also a major emphasis on the development of new approaches and new biotechnology tools.

New Whooping Cough Vaccine: The "DTP" vaccine currently used in this country, although effective in preventing or reducing the severity of pertussis (whooping cough), has significant side effects, mostly swelling at the injection site, fever, and prolonged crying. Seizures and even fatalities have been reported, making some parents hesitant to have their children vaccinated. NICHD scientists have developed a new, single-component vaccine using inactivated pertussis toxin that protects most children who are vaccinated. The new vaccine is highly effective, causes far fewer side effects than the whole-cell vaccine now in use, and requires fewer shots (three rather than five or six) to achieve maximum protection. The new vaccine was tested in NICHD-funded clinical trials. The clinical trials were held in Sweden because it has not recommended vaccination against pertussis since 1979, consequently, whooping cough is endemic. A licensing application for the vaccine has been filed with the FDA for use in the United States. This new pertussis vaccine is now approved for use in Sweden.

New Approach to Cell Culture: Although many types of cells can be grown in conventional tissue culture, such methods provide, at best, a pale imitation of the complex micro environment that influences a cell in the body. One of the challenges of AIDS research is to develop laboratory models that more accurately mirror the disease process in the patient. NICHD scientists have now developed a method of growing living tissue blocks outside the body. These thin block of lymph tissue, which are obtained from tonsillectomies, can be infected with HIV, the AIDS virus, in the laboratory. These advances are helping answer one of the central questions of AIDS pathology — how HIV kills T lymphocytes. One of the leading hypotheses is that HIV makes T cells fuse into large clumps, leading to their death. The scientists have observed widespread cell fusion in the tissue blocks, providing evidence that cell fusion is indeed critical to AIDS pathogenesis. In addition to studies of how AIDS advances, the three-dimensional histocultures will be used to test new drug therapies and immunologic protective strategies against AIDS.

Gene Altered Mice Help Probe Parkinson's Disease, Drug Addiction, Hyper Activity and Schizophrenia: Parkinson's disease is a severe, degenerative condition characterized by a resting tremor, muscular rigidity and difficulty with voluntary motion, which is caused by the destruction of brain circuits involved in the control of movement. The neurons that are destroyed normally secrete the neurotransmitter dopamine. Dopamine-dependent circuits are critical to a broad array of brain functions. Some circuits coordinate movement, but others are part of the "rewards and learning" pathway that is also believed to mediate cocaine and amphetamine addictions, and yet others may be implicated in childhood hyperactivity or schizophrenia. Recognizing the need for animal models with precisely defined defects in these circuits, teams of NICHD scientists, together with other NIH researchers, have succeeded in creating two strains of transgenic mice that each lack a gene encoding a different dopamine receptor (called D_1 and D_3). The D_1 receptor relays nerve signals to the "striatum," a "mini-computer" in the base of the brain that integrates

motor nerve signals coming from the cortex with signals arising from other brain centers, and thus coordinates movement. D₁ "knock-out" mice show a Parkinsonian symptom: They have difficulty rearing up on their hind legs, which seems to mirror the impairment of voluntary movement in Parkinson's disease. They are also reluctant to swallow dry food, but have no difficulty eating "attractive" food like peanut butter. This behavior is likely to be related to the D₁ receptor's role in the brain's "rewards and learning" pathway. Accordingly, the D₁ "knock-out" mice should also be very useful in probing mechanisms by which cocaine and amphetamine become addictive. In contrast, D₂ "knock-out" mice are hyperactive and their rearing behavior is exaggerated, making them an attractive animal model in which to study childhood hyperactivity and possibly schizophrenia. Both mice should also aid in the development of drugs to treat all these disorders — using mice with only one dopamine circuit inactivated at a time would greatly simplify the process of screening potential new drugs for efficacy as well as adverse reactions.

New Type of Tumor Suppressor Gene: Studies of normal developmental processes sometimes shed light on disease processes. Tumor growth occurs either because cell proliferation is overstimulated or because the brakes on growth are not applied. The VHL gene, named after von Hippel-Lindau disease, is one of the newest tumor suppressor genes to be discovered. Von Hippel-Lindau disease is a rare hereditary disorder that predisposes its victims to multiple benign and malignant tumors, primarily of the kidney. Clear cell renal tumors affect more than 20,000 Americans each year. NICHD scientists and their collaborators has revealed a surprising function of the normal VHL gene product. It controls the rate at which transcripts of genes (messenger RNA) elongate by binding to a protein called elongin; elongin promotes transcript elongation. Limiting the rate at which the genetic code is read may be necessary to prevent reading errors from being incorporated into the message. This is the first tumor suppressor gene known to act at this point in the reading of the genetic code — other genes so far identified control the initiation of transcription. The challenge now is to discover how the rate of transcript elongation is related to the control of cell proliferation. An important clue comes from another recent discovery by NICHD scientists. The VHL protein is situated in the nucleus of cultured fibroblasts growing far apart from one another; but when the cells have multiplied to the point where they touch each other, they stop dividing, and the VHL protein, its function probably fulfilled, moves into the cytoplasm. These discoveries have contributed to a better understanding of how gene expression is regulated and shed new light on carcinogenesis.

Genetic Engineering Yields a Diabetic Mouse: NICHD scientists have used genetic engineering to breed a diabetic mouse that is resistant to insulin. Insulin keeps blood glucose levels within defined limits by controlling the uptake and storage of glucose in target cells, such as those in the liver, fat and muscle. Inadequate production of insulin results in type I diabetes mellitus. To regulate glucose uptake, insulin first has to bind to its receptor on the surface of cells. Resistance to adequate amounts of insulin, i.e., insensitivity of target tissues to the hormone, is the primary cause of type II diabetes mellitus, also known as adult-onset or non-insulin-dependent diabetes (NIDDM), which is quite common in older people, particularly if they are overweight. Insulin is also known to play an important role in regulating the growth and development of the fetus, and insulin resistance could therefore explain some cases of fetal growth retardation. To find out whether a defect in the receptor might contribute to insulin resistance, and to define the role of the insulin receptor in utero, NICHD researchers and their collaborators

inactivated the gene for the insulin receptor in mice thus providing an animal model for the study of NIDDM.

EPIDEMIOLOGY, STATISTICS AND PREVENTION RESEARCH

The major areas of research in the Division of Epidemiology, Statistics and Prevention include: congenital malformations, interventions to reduce directly and indirectly the high infant mortality rate in Washington, D.C., investigations of preterm delivery and low birth weight, and research on infectious diseases which affect the health of mothers and children. In addition, adverse health behaviors in mothers and children and possible interventions are being investigated.

Vitamins to Prevent Spina Bifida and Related Birth Defects: It has recently been reported by scientists from NICHD, Trinity College, Dublin and The Health Research Board of Ireland that women with offspring with neural tube defects (NTD) had significantly higher levels of homocysteine in their blood than women with normal offspring. An inability to eliminate homocysteine may be critical in the production of NTDs and folic acid is known to reduce homocysteine, thereby explaining its effectiveness in preventing NTDs. This group has also elucidated a genetic basis for the abnormality in homocysteine metabolism that may explain up to 15 percent of NTD cases. Genetic abnormalities of other enzymes are suspected and are under investigation.

Infant Mortality Initiative: NICHD scientists lead the Infant Mortality Initiative in Washington, D.C. which has implemented several research protocols to address parenting skills in high risk mothers, early childhood determinants of lack of immunization coverage, injuries during infancy, and the impact of components of neonatal intensive care upon neonatal mortality. Other projects are studying barriers to access to prenatal care and an intervention to reduce or prevent adolescent pregnancy.

Group B Streptococcal Infection: Group B streptococcal (GBS) infections are a major cause of neonatal morbidity and mortality in the United States. Consequently there is a search for a safe and effective vaccine. NICHD investigators are collaborating with the Food and Drug Administration in a study of the relationship between maternal serum anti-GBS antibodies at term and the risk of early-onset GBS disease. This study of the protective role of natural immunity, using well-standardized assays, will set benchmarks for evaluating future GBS vaccines.

Enterotoxigenic E. Coli Infections: Diarrhea due to enterotoxigenic *Escherichia coli* (ETEC) is thought to be responsible for about 1 million pediatric deaths annually worldwide. NICHD investigators are collaborating with the U.S. Navy on studies of the first vaccine to be developed against this pathogen. A phase 2 study of the vaccine's safety and immunogenicity has been completed in Egyptian adults. Subsequent phase 2 studies in Egyptian children and infants are planned for the next year, culminating in a large-scale field trial of vaccine efficacy to be done in Egypt.

Preventing Problem Behavior Among Middle School Students: Problem behavior, including use of illegal substances, misconduct, violence and delinquency, increases dramatically during

early adolescence, reaching its peak during the high school years. Youth who develop a positive affiliation with the school develop positive peer relationships and realistic expectations about the outcomes of their actions, and those whose parents monitor their behavior and actively participate in their lives are protected against precocious problem behavior.

The NICHD is testing the efficacy of a multi-component program of school-based interventions in the primary prevention of problem behavior and promotion of prosocial behavior in a sample of middle school students. Interventions are being directed toward (1) students to improve their social skills and comportment; (2) the school environment to increase student participation and bonding; and (3) parents to foster student prosocial behavior.

Research Management and Support

 Authorizing Legislation - Sections 301, Title IV, Subpart 7

1997 Authorization: Indefinite.

FY 1995		FY 1996		FY 1997		Increase or Decrease	
<u>Actual</u>		<u>Estimate</u>		<u>Estimate</u>			
FTE	BA	FTE	BA	FTE	BA	FTE	BA
183	\$26,148,000	180	\$24,294,000	180	\$24,294,000	--	--

The Research Management and Support (RMS) activity provides staff and resources for the administrative management and scientific direction of the Institute. Managerial and administrative services are provided through the following organizational components: the Office of the Director, the Office of Administrative Management, the Office of Science Policy and Analysis, and Communication, and the Office of Grants and Contracts. Scientific direction and administrative management of the Institute's extramural program is provided by the Institute's Scientific Review Program as well as program staff of the Institute's extramural activities.

Funding for the RMS program during the past five years has been as follows:

	<u>Amount</u>	<u>FTEs</u>
FY 1992	\$26,603,000	207
FY 1993	25,214,000	199
FY 1994	26,003,000	188
FY 1995	26,148,000	183
FY 1996	24,294,000	180

Rationale for the Budget Request

The FY 1997 request for RMS is \$24,294,000, the same amount as the FY 1996 estimate. During FY 1997, RMS activity will continue to provide for the professional leadership and technical guidance needed to plan, direct, and implement all programs of the Institute; and to conduct a broad program of information dissemination.

Some specific functions performed by the various components of this program follow. The Scientific Review Program provides policy direction and coordination of review activities within the NICHD involving extramural grant and contract awards. Additionally, this group serves as liaison for applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations. The scientific program staffs of the Center for Research for Mothers and Children, the Center for Population Research, and the National Center for Medical Rehabilitation Research concentrate their efforts on the scientific management of the Institute's grants and contracts.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Research projects						
Noncompeting.....	921	\$211,760	905	\$216,777	890	\$221,502
Admin. supplementals.....	(91)	4,096	(100)	4,500	(100)	4,500
Competing:						
Renewal.....	96	24,382	100	26,631	105	28,300
New.....	168	32,805	188	38,314	192	39,332
Supplemental.....	2	335	2	348	2	355
Subtotal, competing.....	266	57,522	290	65,293	299	67,987
Subtotal, res. proj.....	1,187	273,378	1,195	286,570	1,189	293,989
SBIR/STTR.....	53	9,150	56	9,332	70	11,929
Subtotal, res. proj.....	1,240	282,528	1,251	295,902	1,259	305,918
Research centers						
Specialized/comp. centers.....	77	46,600	77	46,577	77	46,577
Other research						
Research career program.....	102	7,941	103	8,250	103	8,250
Coop. clin. research.....	43	19,816	43	21,095	43	21,095
BRS.....	--	--	--	--	--	--
Minor. biomed. res. support....	--	589	--	606	--	606
Other research related.....	23	2,434	24	3,100	24	3,100
Subtotal, other research....	168	30,780	170	33,051	170	33,051
Total, research grants.....	1,485	359,908	1,498	375,530	1,506	385,546

Training

Individual awards:					
Noncompeting.....	51	1,759	48	1,697	55
Competing.....	44	1,188	48	1,364	41
Subtotal, individ.....	95	2,947	96	3,061	96
					3,121
Institutional awards:					
Noncompeting.....	488	10,750	515	11,821	530
Competing.....	159	4,283	136	3,792	121
Subtotal, inst.....	647	15,033	651	15,613	651
					15,860
Total, training.....	742	17,980	747	18,674	747
					18,981
Research and development contracts (SBIR/STTR)					
.....	93	34,936	98	42,276	96
	(3)	(431)	(5)	(906)	(4)
	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>
					(806)
Intramural research.....	303	70,059	303	73,725	303
					73,725
Research management and support.....	183	26,148	180	24,294	180
					24,294
Total.....	486	509,031	483	534,449	483
					543,441
Clinical Trials.....		(49,112)		(53,000)	
					(53,500)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of Child Health and Human Development

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Population Research..	--	\$129,364	--	\$134,592	--	\$135,729	--	\$140,877	--	\$142,794	--	+1,917
Research for Mothers and Children.....	--	254,759	--	251,236	--	262,277	--	277,233	--	283,320	--	+6,287
Medical Rehabilitation Research.....	--	9,995	--	14,195	--	14,818	--	18,320	--	19,108	--	+788
Subtotal.....	--	394,118	--	400,023	--	412,824	--	436,430	--	445,422	--	+8,992
Intramural Research....	363	69,628	316	69,648	303	69,974	303	73,725	303	73,725	--	---
Research management and support.....	199	25,214	188	26,003	183	26,148	180	24,294	180	24,294	--	---
Total obligations..	562	488,960	504	495,674	486	508,946	483	534,449	483	543,441	--	+8,992
Unobligated balance lapsing.....	--	---	--	45	--	85	--	---	--	---	--	---
Total, budget authority	562	488,960	504	495,719	486	509,031	483	534,449	483	543,441	--	+8,992

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Summary of Changes

1996 Estimated budget authority.....\$534,449,000
 1997 Estimated budget authority.....543,441,000
 Net Change.....+8,992,000

Changes:	1996 Current		Change from Base	
	FTEs	Authority	FTEs	Authority
A. Built-in:				
1. Intramural				
a. Within grade increase.....		\$27,830,000		+\$371,000
b. Annualization of January 1996 pay increase.....		27,830,000		+195,000
c. January 1997 pay increase.		27,830,000		+711,000
d. Payment for centrally furnished services.....		18,115,000		+817,000
e. Service and supply fund increase.....		6,252,000		+138,000
f. Increased costs for services and supplies.....		<u>21,528,000</u>		<u>+474,000</u>
Subtotal.....				+2,706,000
2. Research Management and Support				
a. Within grade increase.....		\$12,021,000		+174,000
b. Annualization of January 1996 pay increase.....		12,021,000		+82,000
d. January 1996 pay increase.		12,021,000		+303,000
e. Federal employees compensation fund; unemployment compensation.....		12,021,000		+6,000
f. Payment for centrally furnished services.....		7,142,000		-459,000
g. Service and supply fund increase.....		3,170,000		+70,000
h. Increased costs for services and supplies.....		<u>1,961,000</u>		<u>+43,000</u>
Subtotal.....				+219,000

Summary of Changes--continued

<u>Changes:</u>	<u>1996 Current</u>		<u>Change from Base</u>	
	<u>Estimate Base</u>		<u>Budget</u>	
	<u>FTEs</u>	<u>Authority</u>	<u>FTEs</u>	<u>Authority</u>
B. Program:				
1. Research project grants:	<u>No.</u>	<u>Amount</u>	<u>No.</u>	<u>Amount</u>
a. Noncompeting.....	905	221,277,000	-15	+4,725,000
b. Competing.....	290	65,293,000	+9	+2,694,000
c. SBIR/STTR.....	<u>56</u>	<u>9,332,000</u>	<u>+14</u>	<u>+2,597,000</u>
Total.....	1,251	295,902,000	+8	10,016,000
2. Research training		18,674,000		+307,000
3. Research and development contracts.....	98	42,226,000	-2	-1,331,000
4. Intramural research.....	303	73,725,000	--	-2,706,000
5. Research management and support.....	180	24,294,000	--	<u>-219,000</u>
Subtotal.....			--	<u>+6,067,000</u>
Total changes.....			--	+8,992,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	483	483	---
Full-time equivalent of overtime and holiday hours.....	3	3	---
Average ES salary.....	\$110,300	\$114,000	+\$3,700
Average GM/GS grade.....	10.6	10.6	---
Average GM/GS salary.....	\$48,900	\$50,000	+\$1,100
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).....	\$80,000	\$81,700	+\$1,700
Average salary of ungraded positions...	\$24,500	\$25,000	+\$500
Personnel compensation:			
Full-time permanent.....	\$19,057,000	\$19,879,000	+\$822,000
Other than full-time permanent.....	5,754,000	6,002,000	+248,000
Other personnel compensation.....	1,185,000	1,236,000	+51,000
Special personnel service payments..	6,938,000	7,238,000	+300,000
Total personnel compensation.....	32,934,000	34,355,000	+1,421,000
Personnel benefits.....	6,627,000	6,913,000	+286,000
Benefits for former personnel.....	290,000	302,000	+12,000

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Travel and transportation of persons...	1,119,000	1,119,000	---
Transportation of things.....	230,000	230,000	---
Rental payment to GSA.....	17,000	17,000	---
Communications, utilities, and misc....	1,641,000	1,641,000	---
Printing and reproduction.....	911,000	911,000	---
Other services:			
Consulting services.....	840,000	840,000	---
Other services.....	6,725,000	6,155,000	-570,000
Purchases from Gov't accounts.....	35,582,000	35,079,000	-503,000
Operation & maintenance of facilities.	4,000	4,000	---
R&D contracts.....	37,962,000	35,985,000	-1,977,000
Medical care.....	1,000	1,000	---
Operation & maintenance of equipment..	1,765,000	1,765,000	---
Supplies and materials.....	7,826,000	7,826,000	---
Equipment.....	5,614,000	5,614,000	---
Lands and structures.....	27,000	27,000	---
Grants, subsidies, & contributions.....	394,204,000	404,527,000	+10,323,000
Insurance claims and indemnities.....	121,000	121,000	---
Interest & dividends.....	9,000	9,000	---
Total budget authority by object....	534,449,000	543,441,000	+8,992,000

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of Child Health and Human Development
Administrative Costs

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	<u>Change</u>
Personnel Compensation:			
Full-time permanent (11.1).....	\$19,057,000	\$19,879,000	+\$822,000
Other than Full-Time Permanent (11.3)....	5,754,000	6,002,000	+248,000
Other Personnel Compensation (11.5).....	1,185,000	1,236,000	+51,000
Special Personnel Serv. Payments (11.8)...	6,938,000	7,238,000	+300,000
Total Personnel Compensation (11.9)....	32,934,000	34,355,000	+1,421,000
Civilian Personnel Benefits (12.1).....	6,627,000	6,913,000	+286,000
Benefits to Former Personnel (13.0).....	290,000	302,000	+12,000
Travel (21.0).....	1,119,000	1,119,000	---
Transportation of Things (22.0).....	230,000	230,000	---
Communications, Utilities, and Miscellaneous Charges (23.3).....	1,641,000	1,641,000	---
Printing and Reproduction (24.0).....	911,000	911,000	---
Consulting Services (25.1).....	840,000	840,000	---
Other Services (25.2).....	6,725,000	6,155,000	-570,000
Purchases from Government Accounts (25.3)...	26,334,000	25,751,000	-583,000
Operation & Maintenance of Facilities (25.4).....	4,000	4,000	---
Operation & Maintenance of Equipment (25.7).....	1,765,000	1,765,000	---
Supplies and Materials (26.0).....	7,820,000	7,820,000	---
TOTAL.....	87,240,000	87,806,000	+566,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

SIGNIFICANT ITEMS IN HOUSE APPROPRIATIONS COMMITTEE REPORT

FY 1996 House Appropriation Committee Report LanguageItem

Nutrition - The House in its report 104-209, page 69 stated..."The Committee is very supportive of the new nutrition research initiatives at NICHD. Of particular significance is the research regarding folic acid and vitamin B-12 use during pregnancy and its reduction in the incidence of neural tube defects among infants. Further research should be supported regarding the role of nutrition in the support of very low birth weight children. The Committee is also supportive of the trial utilizing calcium to reduce the risk of preeclampsia."

Action to be Taken

NICHD researchers involved with the significant study that explained how folic acid could prevent neural tube defects (NTDs) are pursuing this research in an effort to make it possible to develop a screening test to identify women at risk for having children with such a defect. Recently this effort took a large step toward the development of a screening test when it succeeded in identifying a gene responsible for many cases of NTDs.

Further nutrition research that the Institute is pursuing includes studies on the impact of nutrition in the support of very low birth weight babies. Currently the NICHD Neonatal Intensive Care Units (NICUs) Network is developing a common protocol to study this issue. Utilizing the Network of twelve NICUs will enable the Institute to acquire more rapidly the data needed to answer this important research question.

Another area of nutrition research is the Institute's large-scale clinical trial of supplemental calcium to prevent, or reduce the risk of, preeclampsia, a condition characterized by high blood pressure that develops late in the second trimester of pregnancy. Consistent with the Committee's stated support for this study, the NICHD has recently completed the data collection of this trial, which was conducted at five university medical centers. The results of this trial will be made available once the data analyses have been completed.

Item

Sudden Infant Death Syndrome - The House in its report 104-209, page 69 stated..."The Committee is very pleased that the NICHD has vigorously pursued answers to SIDS through its 5-year research plans, and through its successful "Back to Sleep" campaign. The Committee has provided funding for continued activity in this important effort".

Action to be Taken

At the request of the Appropriations Committees, the NICHD developed its first SIDS Five-Year Research Plan for Fiscal Years 1990 through 1994, and its second SIDS Five-Year Research Plan to cover Fiscal Years 1995 through 1999. These plans, developed in collaboration with the SIDS scientific and advocacy community, have provided beneficial guidance, structure, and support to NICHD's SIDS research program. The Institute will continue to keep the Committee informed of its SIDS research progress.

The "Back to Sleep" campaign, a National effort of several major organizations led by the NICHD, is designed to educate the public and professionals about SIDS, how to reduce the risk of SIDS, and how to optimize the health of young infants. When the campaign was launched in mid-1994, nearly 100 percent of infants in this country were sleeping on their stomachs. Today, more than 70 percent are placed on their back or side to sleep; and better than 70 percent of health care providers are recommending the back or side sleep position. Preliminary vital statistics for 1995 have shown a downward trend in the incidence of SIDS. The campaign is continuing with a goal of getting 90 percent of infants placed in the recommended sleep positions in hopes of reducing SIDS significantly. The Institute is pursuing a careful evaluation to determine the impact of the campaign on SIDS, infant care practices, and other health outcomes.

Item

Rett Syndrome - The House in its report 104-209, page 69 stated..."The Committee recognizes and applauds the progress which has been made over the past year in investigating a biological marker for Rett syndrome. The Committee hopes that such findings will lead to greater knowledge of the cause, treatment and cure for this debilitating disease, and encourages continued focus on this area of research."

Action to be Taken

The NICHD has been the leader in Rett syndrome research for a number of years. The Institute has supported several international Rett syndrome research meetings, two large program projects, and other research activities related to the syndrome. NICHD also is making available to researchers Rett patient material through its Brain and Tissue Banks for Neurodevelopmental Disorders. Most occurrences of Rett appear to be sporadic, but some cases suggest a genetic component. With the support of Rett families and research registries, important research is focusing on this question. Some progress has been made in understanding the neuropathology of this disorder, suggesting that it results from abnormal regulation of connections in certain brain regions. Thus, Rett is now believed to be a defect in early development rather than a neurodegenerative disorder. Neuropathology and brain imaging, as well as related studies in animal models, suggest that certain neurotransmitter pathways may be affected. This would seem to indicate that it may be possible to develop pharmacological interventions. Nutritional studies continue to show that high-energy, high-protein supplements result in improved growth and metabolism in affected girls.

Item

Demographic Research - The House in its report 104-209, page 69 stated..."The Committee encourages NICHD to continue giving its demographic research high priority."

Action to be Taken

For a number of years, the Institute has made demographic research a very high priority. Its demographic and behavioral sciences research portfolio provides information on such important issues as the factors that affect trends in premarital childbearing, the determinants and consequences of teen pregnancy, the characteristics of single parent families, immigration, residential segregation, infant mortality, risk-taking behavior, and a number of other topics relating to the growth and changing characteristics of our nation's most valuable asset, its population. This research also focusses on the consequences of demographic trends for the well-being of individuals, families, and society. The Institute will continue to emphasize its demographic and behavioral research activities, and to provide adequate funding for this priority research area.

Item

Autism - The Committee in its report 104-209, page 70 stated..."The Committee encourages NICHD in conjunction with NIMH, NINDS, and NIDCD, to pursue the comprehensive

research recommendations resulting from the conference on autism. Further the Committee will be interested in an update on the Institute's work in this area at next year's budget hearings."

Action to be Taken

Autism research at the NIH is a joint effort of the NICHD, NIMH, NINDS, and NIDCD. With NIH support and leadership, for the first time standard diagnostic criteria have been identified for autism spectrum disorders and incorporated into both the U.S. (DSM-IV) and international (ICD-10) disease and disorder classification systems. The NIH has sponsored three special activities to address this pressing public health problem: First, with the support of the Committee, an NIH Autism State-of-the-Science Conference was held, and a report of the Conference findings and recommendations is being published in the Journal of Autism and Developmental Disorders. Second, highlights of the Conference report were presented to more than 1600 parents and professionals in seminars at the national conferences of the Autism Society of America in Greensboro, North Carolina, and the Autism National Committee in Arlington, Virginia. And third, additional presentations to inform interested individuals about the Conference are scheduled at parent/professional conferences, national workshops for clinicians, and national conferences for parents. The executive summary of the Conference report is available nationwide through the toll-free "fax on demand" system of the Autism Society of America. New initiatives include public/private partnerships between the NIH and the Autism Society of America Research Council, and the NIH and the National Alliance for Autism Research. The NIH will assist these organizations in identifying promising research grants and distinguished fellows in autism research to receive private funding. In addition, an NIH autism RFA has been proposed to carry out the research recommendations of the State-of-the-Science Conference.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amt. Authorized	1996 Estimate	1997 Amt. Authorized	1997 Budget Estimate
Research and Investigation.. Section 301	42\$241	Indefinite		Indefinite	
			\$515,775,000		\$524,460,000
National Institute of Child Health and Human Development.....	Title IV, Part E	42\$285g		Indefinite	
National Research Service Awards.....	Section 487	42\$288	Such sums as necessary	18,674,000 Authorization Pending	18,981,000
Total, Budget Authority...			534,449,000		543,441,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Appropriation History

Year	Estimate to Congress	House Allowance	Senate Allowance	Appropriation ^{1/}
1987	\$309,119,000 ^{2/}	\$368,509,000	\$362,866,000	\$366,780,000
1988	322,032,000	405,673,000 ^{3/}	408,334,000	396,811,000
1989	397,945,000 ^{4/}	407,650,000 ^{5/}	431,388,000	425,649,000 ^{6/}
1990	417,064,000 ^{7/}	448,493,000	450,593,000	449,087,000 ^{8/}
1990 Sequester				-6,173,000
1991	461,473,000	488,282,000 ^{9/}	480,645,000	478,956,000 ^{10/}
1991 Sequester				-6,000
1992	520,584,000	524,661,000	523,826,000	518,251,000 ^{11/}
1993	545,238,000	534,094,000	534,094,000	527,788,000 ^{12/}
1994	542,357,000	555,195,000	555,195,000	554,881,000
^{13/} 1995 Rescission	516,736,000	513,159,000	513,159,000	512,722,000 ^{14/} -687,000
1996	526,177,000 ^{13/}	595,162,000	518,585,000 ^{13/}	595,162,000
1997	543,441,000			

^{1/} Reflects enacted supplementals, rescissions, and reappropriations.

^{2/} The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance spread the funding among the Institutes, including \$2,186,000 for NICHD.

^{3/} Does not include funding for AIDS research. Consolidated at the Secretary's level.

^{4/} The 1989 request excludes funds for AIDS research and education (\$20,443,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

^{5/} Excludes \$14,738,000 in NRSA training programs not considered.

^{6/} Excludes enacted administrative reduction of \$5,739,000.

^{7/} The 1990 request excludes funds for the National HIV program (\$27,129,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

^{8/} Excludes enacted administrative reduction of \$1,506,000.

^{9/} Excludes \$16,562,000 in NRSA training programs not considered.

^{10/} Excludes enacted administrative reductions of \$11,876,000 and \$1,913,000.

^{11/} Excludes enacted administrative reductions of \$180,000, \$5,048,000 and \$973,000.

^{12/} Excludes enacted administrative reductions of \$4,273,000, \$29,000, and \$2,004,000.

^{13/} Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

^{14/} Excludes enacted administrative reduction of \$557,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	5	4	4
Office of the Deputy Director.....	2	2	2
Office of Administrative Management, Office of Research Reporting, Office of Science Policy and Analysis, and Office of Grants and Contracts.....	88	88	88
Center for Population Research.....	29	29	29
Center for Research for Mothers and Children.....	35	33	33
National Center for Medical Rehabilitation Research.....	9	9	9
Division of Scientific Review.....	15	15	15
Division of Epidemiology, Statistics, and Prevention Research.....	27	27	27
Division of Intramural Research.....	276	276	276
Total, NICHD.....	486	483	483

Average GS/GM Grade

1991.....	9.8
1992.....	10.0
1993.....	10.4
1994.....	11.0
1995.....	10.6
1996.....	10.6
1997.....	10.6

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
ES-6.....	1	1	1
ES-5.....	2	3	3
ES-4.....	9	9	9
ES-1.....	1	0	0
Subtotal.....	13	13	13
Total - ES Salary	\$1,474,505	\$1,523,500	\$1,569,000
GS/GM-15.....	44	44	44
GS/GM-14.....	46	46	46
GS/GM-13.....	37	37	37
GS-12.....	40	40	40
GS-11.....	33	33	33
GS-10.....	2	2	2
GS-9.....	24	24	24
GS-8.....	32	32	32
GS-7.....	42	42	42
GS-6.....	20	20	20
GS-5.....	9	9	9
GS-4.....	10	10	10
GS-3.....	4	4	4
GS-2.....	0	0	0
Subtotal.....	343	343	343
Grades established by Act of July 1, 1944 (42 U.S.C.207):			
Assistant Surgeon General.....	3	3	3
Director Grade.....	12	12	12
Senior Grade.....	14	14	14
Full Grade.....	6	6	6
Senior Assistant Grade.....	3	3	3
Subtotal.....	38	38	38
Ungraded.....	13	13	13
Total permanent positions	407	407	407
Total positions, end of year....	504	503	503
Total full-time equivalent (FTE) employment, end of year.....	486	483	483
Average ES level.....	4.0	4.0	4.0
Average ES salary.....	\$107,531	\$110,300	\$114,000
Average GS/GM grade.....	10.6	10.6	10.6
Average GS/GM salary.....	\$47,726	\$48,900	\$50,000



THURSDAY, APRIL 25, 1996.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

WITNESSES

MARVIN CASSMAN, PH.D., ACTING DIRECTOR

G. EARL HODGKINS, FINANCIAL MANAGEMENT OFFICER

W. SUE SHAFER, M.D., ASSOCIATE DIRECTOR, DIVISION OF EXTRAMURAL ACTIVITIES

MARTHA PINE, EXECUTIVE OFFICER

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. DICKEY. The next panel is from the National Institute of General Medical Sciences to discuss their 1997 budget request. The initial witness is Dr. Marvin Cassman, the acting director. If you will, Dr. Cassman, please introduce the others at the table.

INTRODUCTION OF WITNESSES

Dr. CASSMAN. Thank you, Mr. Dickey. To my far left is Earl Hodgkins, our budget officer; next to him is Dr. Sue Shafer, the associate director for extramural activities; and to my immediate left is Martha Pine, the executive officer.

Mr. DICKEY. Welcome.

OPENING STATEMENT

Dr. CASSMAN. Mr. Chairman and members of the committee, I am very pleased to have the opportunity to present to you the programs of the National Institute of General Medical Sciences.

I listen always with admiration and envy to the testimony of my colleagues from the other institutes. The envy arises from their ability to describe the research which they support in terms that are understandable and of direct interest to the public, such as heart disease and stroke and cancer. The research supported by the National Institute of General Medical Sciences ranges from the most fundamental chemistry to pharmacology and physiology and impinges on many different areas of health and disease, but rarely is it immediately related to these areas. Much of the research is done on model systems, such as flies or worms, which are unappetizing, or involve complex molecular systems, that are, to many, incomprehensible. However, the influence of this research is widespread. To illustrate this point, I would like to provide two examples, one qualitative and one quantitative. The qualitative example is a short story presented as a case study of the way basic research supported by NIGMS progresses to application.

For 28 years, beginning in the early 1960s, the NIGMS supported an investigator at Ohio State University who did research on the way metals interact with chemical compounds. He had, as far as I know, no specific interest in biology at all, but we supported him because metals are omnipresent in biological systems, and it was, and is, important to understand their chemistry. Then I have to skip ahead 20 years to the 1980s, when an NIGMS-supported investigator at Johns Hopkins University was looking at proteins that interact with DNA. He found a pattern, which was based on the chemical knowledge that had already been established, that suggested that zinc was bound to the protein in a specific structural form, called a "zinc finger" because of the way the zinc was enveloped by the part of the protein that protruded from the surface, like a finger.

In the late 1980s, three groups supported by the NIGMS independently determined the three-dimensional structures of some of these zinc-binding proteins. They showed that they corresponded to the model earlier proposed, and they further showed how the zinc fingers participated in binding to the genetic materials which they influence. About three years later, an NIGMS grantee demonstrated that these zinc fingers occurred in a protein that was found in the human immunodeficiency virus. Within two years, in 1995—and I want you to notice how the pace is accelerating—this research moved closer to application and consequently moved out of the NIGMS. We no longer support this part of it; it is now supported by the National Cancer Institute in Frederick, Maryland, where it was shown that a class of compounds that bind to zinc could inactivate the HIV virus. Then, just a few months ago a research team at Parke-Davis Pharmaceuticals reported that removal of zinc was indeed the mechanism for inactivation of the virus, and preclinical studies of a family of related drugs to combat AIDS are now underway. These applications could not have happened without the fundamental chemical, biological, and biophysical studies supported by NIGMS over a period of 30 years and more.

Why has the pace picked up so rapidly in moving the fundamental research to applications? Think of a jigsaw puzzle, with each piece being a new discovery. When NIH was first beginning its postwar expansion, most of the jigsaw puzzle was blank, and although each new piece linked up to a few others, a picture was just barely visible. The area covered by basic research had very few connections to the applied areas in biology and medicine. Now, 50 years later, we still have many empty areas to fill in, but the expansion of knowledge ensures that each new piece of basic research makes many connections. Each time it makes connections, many pictures spring into view. These connections include medicine and industrial applications.

As an example of the economic benefits accruing from NIGMS-funded research, you can look at patents as one measure. The primary purpose of the research that we support is the production of new knowledge, and that's very hard to measure. Publications are one index; patents are another. Both of these measures have limitations; but patents in particular can serve as an indicator of invention and technical change. Intuitively one would expect that an institute such as ours which focuses on basic research would not

contribute much to patents. After all, basic research is undertaken "to gain more complete knowledge or understanding of the subject under study, without specific applications in mind." Applied research is targeted to meeting specific, recognized needs, and that's what patents are mostly about.

Nevertheless, in 1993–1994 alone, 1890 patents cited discoveries made by NIGMS grantees as part of the underpinning of the patent, and this remarkably high number of citations is triple that found only six years earlier. This reflects the increased pace of connectivity between basic research and applications that I described previously. Remarkably, some 14 percent of all U.S. patents for drugs and medicines in 1994 cited NIGMS-supported papers. And furthermore, the number of NIGMS citations is the fifth highest when measured against all organizations, including both private and public organizations. It is clear from these data that there are, as I have already noted, an increased number of connections being generated between basic research and applications to medicine as well as industry.

As an indicator of this linkage, investigators and their institutions are increasingly applying for patents based on their own breakthroughs. I will give one example in the field of organic chemistry. Many chemical compounds exist in two forms, which are mirror images. They are called "chiral" compounds, as you can see on the chart to your left. The word "chiral" comes from the Latin, meaning "hand", and, in fact, these mirror images are analogous to your right and left hands. If you put your hands together, you will see that they can't overlap, you can rotate them any way you like and they still remain stubbornly different and mirror images. This is similarly the case with many chemicals. Drugs, for example, are usually active in only one of the two mirror image forms. The other form is either inactive or sometimes can even have deleterious effects. However, when these drugs are synthesized in the laboratory, both forms are usually produced, usually in equal amounts. Clearly, it can be of great importance to develop an approach to make only the therapeutically active form.

NIGMS grantees have been working on this for some time, with several recent successes. One such successful approach is now pending issuance of the patent. Shown on the chart is the progression that illustrates what is happening. The research effort which we supported is something called a Jacobsen epoxidation, shown in this lower left portion of the chart, and is named after the investigator who discovered it, Dr. Eric Jacobsen of Harvard University. It was licensed to a biotech company that made a synthetic chiral intermediate that was then used to make an AIDS drug developed by Merck. I believe this committee has already heard a good deal about these drugs; these are the protease inhibitors which now show so much promise. Generically, what this represents is shown in the middle column. It is the progression from basic research to what is now called chirotechnology, the technology of these chiral intermediates. Through chirotechnology, synthetic intermediates are produced for use in pharmaceutical research to produce drugs that have many health benefits—increased potency, increased specificity, decreased toxicity, and decreased side effects.

The chart presents an indication of the economic benefits of our investment in the underlying basic research. In 1994 our support for research in synthetic chemistry related to this, and to other things as well, was \$26 million. The chirotechnology industry in 1994 had \$1.1 billion in sales of chiral intermediates that contributed to the chiral drugs in the pharmaceutical industry, which in turn in 1994 had \$45 billion in sales. Incidentally, the sales number for chiral drugs in 1994 was a 27 percent increase over the preceding year, which shows you the rapid growth of this area.

Mr. DICKEY. While we're moving that chart over, say that again. What was the increase?

Dr. CASSMAN. It was 27 percent. That is a 27 percent increase in sales of chiral drugs over 1993.

Mr. DICKEY. Do you know what that is in dollar figures?

Dr. CASSMAN. Well, let's see, that would be about a \$9 billion increase in sales from 1993 to 1994.

Mr. DICKEY. Okay. That wakes you up. [Laughter.]

Dr. CASSMAN. Yes. It is a very substantial amount of money. Although we are clearly not the only contributors, we make major contributions.

I would like to point out that I have stressed our contribution through the mechanism of patents because this is an easily measurable and generally accepted indicator of the production and utilization of new knowledge. But I want to make it clear that patents are only a reflection, and they are a pale reflection at that, of the contributions that the basic research supported by NIGMS makes to science and to society. The broad impact of the research emerging from the laboratories of NIGMS-supported investigators goes far beyond patents and can be seen in many fields—from cancer and genetic disorders to immunology and aging. New ideas have a generative force that can't easily be measured but are widely felt, and it is there that the primary contribution of NIGMS exists.

Finally, continued progress requires that new investigators be brought into the research system. We attempt to do this primarily through our training mechanism. Our focus is on predoctoral training through the use of institutional training grants. This approach has recently been affirmed as the preferred mode for training by the National Academy of Sciences report which stated that they are the best mechanism to provide "the development and sustenance of locally conceived program innovations that enhance versatility in the graduate population." The success of these programs has been attested to many times. Evaluations have been conducted about once every decade, and a new evaluation is currently underway at NIH.

The commitment that NIGMS has to training is part of our commitment to maintaining the health of the biomedical research enterprise. Our ability to conduct cutting-edge research will not survive for long if new blood is not continually infused into the body of science.

Mr. Chairman, the fiscal year 1997 budget for the National Institute of General Medical Sciences is \$936,573,000. I would be pleased to answer any questions that you might have.

[The prepared statement and biography of Dr. Marvin Cassman follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement of the Acting Director

National Institute of General Medical Sciences

Mr. Chairman and Members of the Committee, I am pleased to present to you the programs, progress, and plans of the National Institute of General Medical Sciences (NIGMS).

I listen with admiration and envy to the testimony of my colleagues from the other Institutes. The envy arises from their ability to describe the research which they support in terms that are understandable and of direct meaning to the public - such as heart disease, stroke, and cancer. The research supported by NIGMS ranges from the most fundamental chemistry to pharmacology and physiology and impinges on many different areas of health and disease, but rarely is it immediately related to these areas. Much of the research is done on model organisms, such as flies or worms, which are unappetizing, or involves isolated molecular systems, that are, to many, incomprehensible. In order to illustrate the widespread influence of this research I would like to provide two examples, one qualitative and one quantitative. The qualitative example is a short story, presented as a case study of the way basic research supported by NIGMS progresses to application.

From Basic Research to Applications

For 28 years, beginning in the early 1960's, NIGMS supported an investigator at Ohio State University who did research on the way metals interacted with chemical compounds. He had no specific interest in biology at all, but we supported him because metals are omnipresent in biological systems, and it was, and is, important to understand their chemistry. In the 1980's, an NIGMS-supported investigator at Johns Hopkins University who was looking at proteins that interact with DNA found a pattern that suggested that zinc was bound to the protein in a specific structural form, called a "zinc finger". In the late 1980's and early 1990's, three groups supported by NIGMS independently determined the three-dimensional structures of some of these zinc-binding proteins, showed that they corresponded to the model earlier proposed, and further showed how the zinc fingers participated in binding to the DNA. About three years later, an NIGMS grantee demonstrated that these zinc fingers occurred in a protein that was found in the human immunodeficiency virus. Within two years, in 1995 -- notice how the pace accelerates -- a group at the National Cancer Institute in Frederick, Maryland, showed that a class of compounds that bind to zinc could inactivate HIV, and just a few months ago a research team at Parke-Davis Pharmaceuticals demonstrated that removal of zinc was indeed the mechanism for inactivation of the virus. Preclinical studies of a family of related drugs are now under way. These applications could not have happened

without the fundamental chemical, biochemical, and biophysical studies supported by NIGMS over a period of 30 years and more.

Why has the pace picked up so rapidly in moving the fundamental research to applications? Think of a jigsaw puzzle, with each piece a new discovery. When NIH was just beginning its postwar expansion, most of the jigsaw puzzle was blank, and although each new piece linked up to a few others, the picture was barely visible. The area covered by basic research had very few connections to the applied fields of biology and medicine. Now, 50 years later, we still have many empty areas that need to be filled in, but the expansion of knowledge ensures that each new piece of basic research makes many connections, including connections with medicine and with industrial applications.

Economic Benefits

The quantitative measure of the impact of NIGMS-funded research comes from a look at patents. The primary purpose of NIGMS-funded research is the production of new knowledge, which is very hard to measure. Publications are one index, and patents are another. Both of these measures have limitations, but patents in particular can serve as an indicator of invention and technical change. Intuitively one might expect that an Institute such as the National Institute of General Medical Sciences, which focuses on basic research, would not have a high patent rate. After all, basic research is undertaken "to gain more complete knowledge or understanding of the subject under study, without specific applications in mind", while applied research is considered to be targeted to meeting a specific, recognized need, and it is those specific needs that are reflected in patents.

In fact, NIGMS-supported research has made significant contributions to the practical applications that are reflected in patents. In 1993-1994 alone, 1890 patents cited discoveries made by NIGMS grantees as part of the underpinning of the patent, and this remarkably high number of citations is triple that found only six years before. -- This reflects the increased pace of "connectivity" between basic research and applications that I described earlier. -- Some 14% of all U.S. patents for drugs and medicines in 1994 cited NIGMS-supported papers. Further, the number of NIGMS citations is the second highest of all the Institutes at NIH, and it is the fifth highest when measured against all organizations, public or private. Why have the basic research efforts supported by NIGMS had such a significant effect on practical outcomes as reflected by patents? It is because the effort to understand the fundamental nature of biological systems is closely linked to the desire to find applications for the concepts that emerge. It is important to recognize that basic research and the application of the research are inextricably linked.

Increasingly, investigators and their institutions are applying for patents based on their own breakthroughs. I will give one example in the field of organic chemistry. Many chemical compounds exist in two forms, which are mirror images. These are called "chiral" forms. They are analogous to your right and left hands. In nature, only one form usually exists, and drugs are active in only one of the two forms. The other form is either

inactive or sometimes can even have deleterious effects. However, when these compounds are synthesized in the laboratory, both forms are usually produced, often in equal quantities. Clearly, it can be of great importance to develop an approach to make only the active form. NIGMS grantees have been working on this for some time, with several recent successes. One such successful approach is now pending issuance of the patent. The fundamental discovery, which we supported, is a chemical reaction named after its discoverer, Dr. Eric Jacobsen, from Harvard University. The process has been licensed to a biotech company, which produced a key molecule that served as an intermediate in the synthesis of a new anti-AIDS drug. This drug is now demonstrating considerable promise in extending survival in individuals with advanced AIDS. This is one specific example of basic research leading to a new industry, chirotechnology, which ultimately leads to a variety of health benefits arising from these new drugs - - increased potency of the drug, increased specificity, decreased toxicity, and decreased side effects.

It is worth mentioning that the industry based on these chiral drugs is growing rapidly. The NIGMS investment of about \$26 million a year in all of synthetic organic chemistry, helped to generate, in 1994, a chirotechnology industry with about \$1.1 billion in sales, and a chiral drug market with \$45.2 billion in sales in 1994, an increase of 27% over 1993.

I have stressed our contribution through the mechanism of patents because this is an easily measurable and generally accepted indicator of the production and utilization of new knowledge. However, I want to make it clear that patents are only a reflection - and a pale reflection at that, of the contributions that the basic research supported by NIGMS makes to science and society. The broad impact of the research emerging from the laboratories of NIGMS supported investigators goes far beyond patents, and can be seen in many fields ... from cancer and genetic disorders to immunology and aging. New ideas have a generative force that can't easily be measured but are widely felt. It is there that the primary contribution of NIGMS exists.

Research Training

As part of our commitment to ensuring the existence of a highly trained workforce, NIGMS has a major involvement in predoctoral research training. This activity is primarily through the means of training grants given to institutions. Our approach was reaffirmed by a recent National Academy of Sciences report as the preferred mode for research training, since "They have been used effectively to meet a variety of national objectives, and they can be tuned to the goal that we (NAS) emphasize: the development and sustenance of locally conceived program innovations that enhance versatility in the graduate population." This describes quite well the intent and practice in the primary mechanism we use to support training. Although we define some quite broad interdisciplinary fields of interest, in other respects we rely on the institutions themselves to define their "locally conceived program innovations" which "enhance versatility". We require of the applicants that the programs be interdisciplinary, that appropriate mentoring is provided, and that the students are permitted to draw from a

broad pool of faculty who cross departmental boundaries. We also require a commitment to recruit underrepresented minorities and to insure appropriate training in scientific ethics. Beyond that, we expect, and get, a wide variety of approaches to training.

These programs are limited to a small number of the highest quality institutions, and even at most of those institutions only a small percentage of the graduate population in the biomedical sciences is supported. The intent is to insure the quality of the training, through programmatic requirements and through evaluation of the training faculty and the student populations. The rigorous peer review the applications receive make them the gold standard for training and have an effect far beyond the limited numbers of students supported. The success of these programs has been attested to many times, as evaluations have been conducted about once every decade since their initiation and have consistently demonstrated that our predoctoral trainees do better, based on a number of criteria, compared to control groups. A new evaluation of NIH training is now under way, and the first phase is expected to be completed this year.

The commitment that the NIGMS has to training is part of our commitment to maintaining the health of the biomedical research enterprise, as reflected in our concern for bringing a cadre of well-trained new investigators into the research system, both through training and research mechanisms. Our ability to conduct cutting-edge research will survive as long as new blood is continually infused into the body of science.

Minority Support

The NIGMS programs that focus on stimulating the involvement of underrepresented minorities in science cover both support for research and for training. Our long-standing training program, and the best known, is the Minority Access to Research Careers, or MARC, Program. At the request of Congress, we have recently completed an evaluation of this program. We conducted a series of surveys to gather information on the outcomes of the MARC program. The major conclusions of the report show that students derived significant benefits from participating in this program. For example, the MARC students have pursued and obtained graduate degrees at greater rates than minority bachelor's degree recipients who were not in the program. However, we have not had much effect on increasing the numbers of minority students going on to the Ph.D., either at many of the institutions we support or nationally. It is still a distressing fact that the percentage of minorities receiving the Ph.D. in the biomedical sciences remains at the same low level that it has been for at least the past decade. We are currently expanding our efforts through new initiatives to try and make some headway in increasing the numbers of minority Ph.D.'s by strengthening the capabilities of institutions to recruit and retain qualified students and by enhancing their research and training efforts.

Mr. Chairman, the fiscal year 1997 budget request for the National Institute of General Medical Sciences is \$936,573,000. I would be pleased to answer any questions that you might have.

CURRICULUM VITAE

NAME : Marvin Cassman, Ph.D.

POSITION : Deputy Director, NIGMS

BIRTHPLACE : Chicago, Illinois
AND DATE : April 4, 1936

EDUCATION : B.A., 1954 (Liberal Arts) University of Chicago
B.Sc., 1957 (Anatomy) University of Chicago
M.S., 1959 (Biochemistry) University of Chicago
Ph.D., 1965 (Biochemistry) Albert Einstein School of
Medicine

EXPERIENCE : 1989 - Present Deputy Director, National Institute of
General Medical Sciences, (NIGMS), NIH

1985-1989 Director, Biophysics and Physiological
Sciences Program, NIGMS, NIH

1985-1986 Senior Policy Analyst, Office of Science
and Technology Policy, Executive Office
of the President

1978-1984 Chief, Molecular Basis of Disease Section,
Cellular and Molecular Basis of Disease
Program, NIGMS, NIH

1975-1978 Health Science Administrator, Cellular and
Molecular Basis of Disease Program,
NIGMS, NIH

1967-1974 Assistant Professor, University of
California, Santa Barbara

1965-1967 NIH Postdoctoral Fellow, University of
California, Berkeley

1959-1961 Research Fellow, Northwestern University
Medical School

HONORS AND
AWARDS : 1991 Presidential Meritorious Executive Rank
Award

1983 NIH Director's Award

BRIDGE FUNDING

Mr. DICKEY. Thank you, sir. I have several questions. Your institute is experimenting with the concept of putting a small tax on grants funding to provide bridge funding for competing renewal grants that fall 10 percentile points below the pay line. Tell us why you decided to try this approach, and what the length and size of grants will be.

Dr. CASSMAN. We did an analysis to see just what happens to people who miss the pay line, who are not funded but are close to being funded. It turns out within the range that you just mentioned, within 10 percentile points of our payline, about 65 percent get funded within a year of the time they lose their support. These are very high quality applications, 85 percent of them fall within the top 15 to 20 percent of all the applications received. This means that extremely high quality projects are having their research seriously disrupted for the year in which they go without any funding at all. Consequently, we felt it would be useful to provide them, as interim funding for one year's time, an amount equal to roughly one-third of their previous year's award to allow them to survive for that period of time until, as we have seen, many of them get funded again.

We expect the average reduction to ongoing grants to make this bridge funding possible for others will be about one-half of 1 percent. It will have no influence at all on the length of the ongoing grant awards.

Mr. DICKEY. Dr. Varmus, do you think this approach has a potential for broader use on the campus?

Dr. VARMUS. It is being used. In fact, there are various ways in which that general approach is being used. Dr. Klausner described yesterday a mechanism that he's using which is a little bit different in character. What he's doing is inviting applicants whose grants are close to the pay line to submit a response to the initial review group's criticisms. That response is then reviewed by experts on his staff who, if satisfied with the response, will actually fund the grant in advance of what would usually be a lengthy nine month process. So we're quite concerned about those folks who have active research programs and fall just below the pay line in their renewal applications, because we know that this disruption of their research endeavors can be quite costly and, of course, will result in a loss of useful information.

NEW INVESTIGATORS

Mr. DICKEY. Thank you. Dr. Cassman, you have done some analysis of trends over time in the age of researchers applying for grants and the number of grants received per principal investigator. Can you tell us what you have found? Is there a problem with the rate at which new investigators are entering research?

Dr. CASSMAN. Yes, we feel that there is a problem. At least in our institute, we found that despite our best efforts, and we make great efforts to bring in new investigators, the percentage of our total funded investigators that are new investigators has been dropping, slowly but still dropping, over the last 10 years.

The age distribution is another issue that is very worrying, although it is not entirely clear what we can do about it. I have a chart here that I will be happy to provide to you that shows the gradual, but inexorable increase of the age of new NIH grantees; these are people who are just getting their new awards. It has been going up steadily since 1979 at least. This is probably due to a combination of many factors and we do not have complete control over them.

Mr. DICKEY. Are those investigators basically Americans or are they foreigners?

Dr. CASSMAN. I couldn't give you a direct answer as to how many of these are foreign born. I would say that most of them, in fact, are American, but I can't give you a breakdown.

Mr. DICKEY. Dr. Varmus, did you have something you wanted to say about that?

Dr. VARMUS. No. But I agree with Dr. Cassman that while we do have many trainees here on temporary visas, virtually all of our grantees are either American born or naturalized citizens.

PAYING GRANTS ON A SLIDING SCALE

Mr. DICKEY. Dr. Cassman, you have also floated the idea of using a sliding scale to pay grants, with the top scoring grants receiving full funding and grants in the next percentile as being paid some fraction of their cost, like 80 or 90 percent. The object of this exercise would be to fund more new grants than otherwise would be the case. What has been the reaction of the scientific community to your proposal?

Dr. CASSMAN. Well, first, I should say that was only an option that we considered. We looked at using a sliding scale very carefully and did an analysis and we felt that it was not a practical approach. The amount that we would have to reduce investigators at the bottom of the scale would simply be too much to provide a significant benefit in extending the payline to fund more applicants. Rather than doing that, we're considering the mechanism that you've already discussed, that is, providing interim or bridge funding for a larger group for a shorter period of time.

SUCCESS RATE

Mr. DICKEY. You and Mr. Porter have talked about this in the past, but how do you continue to maintain a higher than average success rate, 35 percent in 1996, for your grant portfolio?

Dr. CASSMAN. That is simply because that's where we put all our money. Roughly 80 percent of our budget goes into investigator-initiated grants, the so-called research project grants. We put less than 1 percent into centers, perhaps a half a percent into contracts, and perhaps this would be a useful point to mention, that we have a management support cost of only 2.6 percent, which is really quite remarkably low as well.

ADMINISTRATIVE COSTS

Mr. DICKEY. It sure is. The share of your total budget allocated to administrative costs, research management and support is well

below the NIH average. What approaches do you use to constrain these costs?

Dr. CASSMAN. We have used a lot of central NIH services rather than having our own. For example, we do not have our own contracts office. Similarly, we use the central NIH procurement office, and we are establishing now, or participating in a number of competitive service centers as well. That's at least part of the way we've managed to keep our administrative costs so low.

RESEARCH TRAINING

Mr. DICKEY. In the ongoing debate about whether we're training too many researchers for the jobs available, those who favor downsizing the Federal training role contend that the research community will never support a decrease in training because it provides principal investigators with a steady source of cheap labor that allows them to apply for more grants. Do you think this criticism has any merit?

Dr. CASSMAN. The research community has supported a very considerable decrease in the past twenty years in our level of effort. There remains a need for well-trained biomedical scientists, although it is clear that the demand is not what it was when the training programs began in the 1960s. But at its peak, we supported about 9,000 trainees; we now support about 3,000. That's a reduction of two-thirds already. At its peak, the percentage of our budget which went to training was 35 to 45 percent; it is now 11 percent. I think it is important to mention we train for the future, not for the present. The students who are entering graduate school now will be looking for their jobs 8 to 10 years from now. And I should point out that the track record of prognosticators in predicting supply and demand has not been very good. I believe that, as a consequence, the degree of investment that we currently have is prudent and appropriate.

Mr. DICKEY. With all the downsizing and discussions about downsizing, how has the morale been among young trainees?

Dr. CASSMAN. It is not good in many places. Students are worried, they're concerned about their futures, they don't know what kinds of jobs will be available to them.

RESEARCH TRAINING STIPENDS

Mr. DICKEY. The President's budget proposes a 2.2 percent increase in research training stipends. Why did NIH choose to increase stipends this year? Does it reestablish parity with training programs sponsored by the National Science Foundation and others?

Dr. CASSMAN. We're actually nowhere near parity with most of the other agencies. The differential is variable, but we're on the low end every time. The reason for the increase? We need to have a gradual and continuous increase to keep up with inflation. The pattern of the past has been a period of holding stipends flat and then a jump and then a flat period again. This is really not the best way to do it.

RESEARCH TRAINING TUITION REIMBURSEMENT

Mr. DICKEY. The NIH task force on tuition policy for research training grants issued its recommendations last fall. Can you summarize their major recommendations and tell us how the NIH leadership has responded to them.

Dr. CASSMAN. The primary recommendation is to ensure a uniform tuition reimbursement policy of payment of full costs up to \$2,000 and 60 percent after that. This recommendation has been accepted.

IMMIGRATION OF SCIENTISTS

Mr. DICKEY. A January article in "Science Magazine" indicated that immigration into the U.S. among those in the science and engineering disciplines has increased by 80 percent from 1991 to 1993. Legislation has been floated to limit legal immigration in these categories. While such a concept is controversial within the U.S. scientific community, some younger scientist organizations favor it, given the stiff competition for grants and jobs. How do you think we should approach this issue?

Dr. CASSMAN. The concerns of the younger scientists are clearly understandable. However, the United States competes scientifically and for scientific personnel worldwide; this has been true for a long time. There are American scientists who wind up going to Europe and elsewhere, and America gets the best of some of the foreign scientists as well. I was at an awards ceremony yesterday for the Fermi Award; it's the highest medal for physics that's given in this country. The two recipients were both foreign born and have been American citizens for long periods of time. We have had enormous benefits from immigration to this country of highly trained people. I would be very cautious about any actions that would stem that.

STRUCTURE-BASED DRUG DESIGN

Mr. DICKEY. Your institute as well as the National Center for Research Resources has a role in encouraging structure-based drug design. Have any successful drugs been designed by computer to date?

Dr. CASSMAN. Many successful drugs have been designed with input from this technology. I'm not really sure that there are any that have actually been designed from their very beginnings just on the basis of structure alone. But certainly every pharmaceutical company in the world probably now has a structural research component that provides information and guidance in the design of drugs. So it has had a major effect.

Mr. DICKEY. Those are all the questions we have. We want to thank you all for coming. This committee is in recess until 2:00, unless Mr. Stokes has something to say. Do you have any questions? This is the dean of the committee right here.

MINORITIES' PURSUIT OF ADVANCED DEGREES AND SCIENTIFIC CAREERS

Mr. STOKES. Good morning. You said that the evaluation of the MARC program has shown that the program is successful in encouraging minority students to enter science. However, it does not

seem to increase the number of minorities obtaining Ph.D.s. Does that mean the minority students tend to leave academics after obtaining a master's degree?

Dr. CASSMAN. No, I don't think that's the reason. Certainly, about 16 percent of the MARC students have gotten master's degrees, but many more have gone on to Ph.D.s. or M.D.s. It is simply the numbers aren't high enough. We have not increased the numbers that are going through the Bachelor's degree program and then on to get the Ph.D. The students who have been in the MARC program have been very successful compared to their peers in completing their degrees. There just aren't enough of them.

Mr. STOKES. Do you have any information on whether they stay in scientific fields even without a doctoral degree?

Dr. CASSMAN. Yes, I do have the data. I don't believe I have it immediately available. Most of them, approximately two-thirds, do stay in scientific fields, Mr. Stokes.

MEDICAL SCIENTIST TRAINING PROGRAM

Mr. STOKES. The Federation of American Societies for Experimental Biology in its 1997 budget recommendation advocates increasing the number of joint M.D./Ph.D. candidates trained. Does the President's 1997 budget reflect this recommendation?

Dr. CASSMAN. No, it does not.

RESEARCH ON DISEASE-RESISTANT RICE

Mr. STOKES. Doctor, your institute has supported research to genetically engineer disease-resistance into plants, in this case rice. Why does NIGMS support this sort of research, which sounds a little more appropriate for the Department of Agriculture?

Dr. CASSMAN. This was a spin-off of the research that we've funded. The research project was not really directed to improving rice yields. It was, like many other projects, fundamental research into certain genetic characteristics. In one instance, the model that was used was rice, but it happens that the funding was fortuitous. We did not support the research for the purpose of improving the rice yield.

NEW MARC PROGRAM ANNOUNCEMENT

Mr. STOKES. Doctor, I understand that the institute has issued a program announcement that includes new guidelines for institutional eligibility for the MARC program. I am extremely concerned, as your institute is authorizing institutions to use their own criteria to establish eligibility. Explain to us how this change is in the best interest of those institutions, and the students that attend them.

Dr. CASSMAN. The eligibility criteria have not changed at all. They are still the same as they have been. We are now asking the institutions simply to tell us how they can best achieve the goals of the program, which is to produce more Ph.D.s. As I'm sure you know, Mr. Stokes, the institutions in the MARC program are quite diverse. Some of them are very research-intensive universities; others are much smaller, closer to liberal arts colleges. They can't all have the same approach to educating students and they can't all

have the same goals. We're simply asking them to develop their own goals and their own ways of reaching those goals. But the eligibility criteria remain exactly the same.

Mr. STOKES. So in your opinion, you're not in any manner changing the legislative intent of that program?

Dr. CASSMAN. Absolutely not. The same population of schools is involved. There is no change at all.

Mr. STOKES. Can you give us some idea of what process was utilized to arrive at the new guidelines?

Dr. CASSMAN. The new director of the MORE Program, the Minority Opportunities in Research Program, Doctor Clifton Poodry, held a series of meetings over the course of about a year, including discussions with the program directors of both the MARC and the MBRS programs and with special panels of educators and interested people that he convened to discuss all of these issues.

Mr. STOKES. Were the grantees involved in this process?

Dr. CASSMAN. Many of them, yes, at the program director's meeting. This was a year ago prior to the establishment of the new guidelines.

Mr. STOKES. And as a consequence of this, then, they all received notification relative to the change in the guidelines, is that correct?

Dr. CASSMAN. Yes, they did.

MARC EVALUATION

Mr. STOKES. While the Institute's study of the MARC program is interesting, the self-reporting data used seems questionable. In fact, a new study seems warranted since many of the negative inferences are not compatible with the NIH's prior reports on the success of the MARC program. How would you respond to this statement?

Dr. CASSMAN. Any retrospective study is difficult. What you have to do is contact the people involved, track them down, get them to respond to questionnaires. In many cases, we had to contact them personally over the telephone. We are trying to build in to our programs now prospective evaluations that allow us to start gathering data on program participants from the beginning and track things forward. But I don't believe that the data that was reported in the MARC study is in error. The questionnaires were generally quite straightforward. Certainly, the numerical data which we obtained from our own records is I believe quite accurate.

Mr. STOKES. Who requested the study?

Dr. CASSMAN. The study was initiated by the Institute following a recommendation from the National Academy of Sciences. We are in the process of sequentially looking at all of our training programs. We began a year ago a study of the Medical Scientist Training Program, the MSTP program, as well.

Mr. STOKES. Let's go back to the study for a moment. What was the purpose of the study?

Dr. CASSMAN. To identify the successes and, to the extent that we could, the limitations of the MARC program.

Mr. STOKES. And what outside organization conducted the study?

Dr. CASSMAN. I don't remember. We will supply it for the record. We had two organizations involved in different phases of the project, including data collection.

[CLERK'S NOTE.—Subsequent to the hearing, NIGMS corrected this figure to "three organizations," for the record.]

[The information follows:]

CONTRACTORS INVOLVED IN THE MARC STUDY

The Research Triangle Institute (RTI), Research Triangle Park, NC, prepared the preliminary study design for the MARC study. RTI is a well-established and nationally-recognized firm that conducts social science research and evaluation studies for a variety of Federal agencies. RTI was selected from a small, select group of firms which had competed successfully for evaluation task order contracts with the U.S. Department of Health and Human Services.

The RTI study design was reviewed, revised somewhat, and implemented by a team of two contractors whose staff are knowledgeable about issues surrounding the education of minority students in the sciences and experienced in performing evaluation studies: KRA Corporation, of Silver Spring, MD, and R.O.W. Sciences, Inc., of Rockville, MD, both minority-owned firms. Together they did the data collection.

The final data analysis and preparation of the study report was completed by R.O.W. Sciences, Inc., which has successfully conducted numerous program evaluations for the Federal government.

Mr. STOKES. Can you give us some idea of the criteria and what instruments were used to measure either success or failure?

Dr. CASSMAN. It was a questionnaire that was developed. Obviously, there were lots of things we would have liked to ask that we felt we couldn't because when you start making questionnaires too long, people throw them away. So we tried to focus on the specifics; which is, what were the educational and career outcomes of the students who went through the MARC program. Those were the primary outcomes that we evaluated—where did they go, what were they doing, what fields were they in.

Mr. STOKES. Are you saying to me that rather than criteria, that what you utilized here was a questionnaire?

Dr. CASSMAN. Well, yes. The questionnaire embodied the criteria which we developed. The question we were asking was what happens to MARC students; that is, what are their educational and career outcomes. And that's what we attempted to answer predominantly through this survey.

MBRS PROGRAM

Mr. STOKES. I understand that program directors, attending the Institute's meeting in March, were most concerned about the individuals the MBRS program uses to review their applications. I also understand the general consensus is that individuals from majority institutions should not be used, but rather scientists from minority institutions. What is the system and criteria used to select reviewers? And to what extent has this changed under your directorship?

Dr. CASSMAN. The review groups review the science. We use panels that look at specific areas of science that are represented in the MBRS grant applications. The panelists are from both majority and minority institutions. Most of them are, in fact, from the same institutions that are being reviewed, or from minority institutions comparable to those whose research proposals are being reviewed. Our focus is on people who understand the science. In that respect, it is important to have people who are from both majority institutions and minority institutions looking at the research.

Mr. STOKES. I have been advised, and you can correct me if this information is incorrect, that approximately 30 percent of the

MBRS budget is awarded to institutions on the Island of Puerto Rico, that the next largest number of recipients are institutions in New Mexico, Texas, and California. Firstly, is this true?

Dr. CASSMAN. There certainly is a substantial representation from Puerto Rico. I couldn't tell you whether it's 30 percent, I'll have to give you that number for the record. The other distributions of course reflect the Hispanic-serving institutions, many of which are in Texas and New Mexico and a number of which are also in California.

Mr. STOKES. But, isn't this occurring to actually decrease the amount of funding that formerly went to historically black colleges and universities?

Dr. CASSMAN. Our funding to the HBCUs has gone up steadily. In 1996, it is essentially the same amount as it was last year. It is considerably higher than it was prior to that. I think our direct funding has been pretty consistent to HBCUs and, in fact, the number of HBCU institutions receiving our funding has stayed essentially constant over the years.

Mr. STOKES. So that we can get a clear understanding, tell us what percent of the MBRS awards, in dollars, go to HBCUs.

Dr. CASSMAN. I don't have that particular piece of information for MBRS with me. Forty-seven programs out of 95 programs are HBCUs, equal to about 50 percent, and it is roughly the same amount for the MARC program, a little over 50 percent. I'm not sure I have the dollar number at the moment, just the number of applications.

Mr. STOKES. I would like to have the record reflect that data for both of these programs. That information will give us some understanding of what the revenue stream has been and what it is now. Will you do that, please?

Dr. CASSMAN. Of course. I'd be happy to provide that.

[The information follows:]

MBRS AND MARC SUPPORT FOR SPECIFIED INSTITUTIONS

	FY 1990		FY 1995	
	Dollars	Percent	Dollars	Percent
MBRS:				
HBCU's ¹	19,883	49	19,569	41
Non-HBCU's in:				
Puerto Rico	4,369	11	6,258	13
Texas	2,568	6	3,096	6
New Mexico	1,616	4	2,086	4
California	3,361	8	8,209	17
MARC:				
HBCU's ¹	4,577	45	7,853	56
Non-HBCU's in:				
Puerto Rico	547	5	1,451	10
Texas	257	3	763	5
New Mexico	127	1	468	3
California	846	8	1,442	10

¹ Funds for Historically-Black Colleges and Universities, including those in the three states and Puerto Rico listed above.

CHANGE IN MBRS GRANT CEILING

Mr. STOKES. I understand that you have lifted the \$1.5 million ceiling on funds that can be requested for an individual MBRS program. Is that correct?

Dr. CASSMAN. That's correct.

Mr. STOKES. Does this not put small institutions at a disadvantage since large institutions are substantially more developed, and can command most of the available funds?

Dr. CASSMAN. We feel that we can give the small institutions the revenues that are appropriate to their needs. What we have found, however, is that the larger institutions which have been in many ways the most productive in achieving the goals that we want, which is to produce more under-represented minority Ph.D.s, have been starved for funds. The \$1.5 million cap has been an arbitrary restriction on the effective usage of the dollars from some of the best schools that participate in the program. We really need to strengthen the best as much as to help support some of the smaller ones.

Mr. STOKES. Let me understand Dr. Cassman. You say, you really need to strengthen the best institutions as well as what others?

Dr. CASSMAN. As well as to maintain some support at the smaller institutions that don't have the same capacity and, in fact, are not really oriented toward research in many cases at all. They are primarily teaching institutions.

Mr. STOKES. Dr. Cassman, that completes the questions for this morning's hearings. Thank you very much.

The committee now stands in recess until 2:00 p.m. this afternoon.

[The following questions were submitted to be answered for the record:]

MARC AND MBRS SUCCESS RATES

Mr. Porter: An article in the January issue of the Journal of NIH Research reported that success rates for the MBRS and MARC grants were well above average. Does this concern you, or indicate that perhaps some resources should be reallocated to areas that have much lower success rates?

Dr. Cassman: The success rate for the MBRS Program reflects, in part, the fact that, in peer review, MBRS applications are assessed against criteria of merit unique to this program. Those criteria reflect the developmental thrust of the Program, that is, the emphasis on building research capability in minority institutions, in their faculty, and in their students majoring in relevant areas of science. In addition, appropriated funding levels for this program and the historically strong interest on the part of both the Congress and the Executive Branch in building this research capability at minority institutions have led to this higher success rate. The success rate for the faculty fellowship mechanism of the MARC Program, cited in the article, varies dramatically from year to year, due to the relatively low number of applications submitted and differences in how these few fare in peer review. Given the nature of these programs, the success rate seems to be appropriate.

MARC STUDY

Mr. Porter: Provide a summary of the major points of the recently completed evaluation of the MARC Program.

Dr. Cassman: The major findings of the MARC study are presented below:

- MARC students have pursued and obtained graduate degrees at greater rates than minority bachelor's degree recipients in biology and chemistry who did not participate in the MARC Program. Forty-eight (48) percent of former MARC students have sought masters or Ph.D. degrees. The comparable figures for minority and majority baccalaureates are 19 percent and 23 percent, respectively.
- A substantial number of former students have already obtained research doctorates. A greater percentage of former MARC students receive the Ph.D. (approximately 15 percent) than do other minority and majority baccalaureates in biology and chemistry (4 and 12 percent, respectively)
- Among MARC students attending graduate school, approximately 33 percent receive terminal masters degrees in the biological, physical, or health sciences.
- As a result, the percentage of MARC students entering graduate school who eventually receive a doctorate is similar to the overall percentage among all minority students entering graduate school (28 and 22 percent, respectively). Both are substantially below the percentage of majority graduate students who receive a doctorate (50 percent).
- Former MARC students who obtained Ph.D.s did so in approximately 1 year shorter time from receipt of the baccalaureate than did other minority Ph.D. recipients in the biological sciences.
- Approximately twice as many MARC students have obtained clinical doctorates than have received research doctorates. Among underrepresented minorities, only Hispanics have sought research doctorates at a greater rate than clinical doctorates.
- Although former MARC students have been successful, there have been no discernible increases as a result of MARC funding in the numbers of students from MARC institutions who go on to receive Ph.D.s or M.D.s.
- Two-thirds of former MARC students are employed in the biological, physical, or health sciences. Forty-one (41) percent are employed in academia and 75 percent of these are involved in research.

BRIDGES PROGRAM

Mr. Stokes: The Institute has been administering a Bridges to the Future Program for approximately four years. The program is funded by the NIH Office of Research on Minority Health. What is the current status of the program?

Dr. Cassman: The first nine awards made under the Bridges to the Future Program were made in fiscal year 1992. To date, a total of 61 grants have been made, 42 of which have supported bridges from colleges awarding Associate Degrees to four-year baccalaureate degree granting institutions and 19 of which have supported bridges from institutions awarding the Masters degree to institutions awarding the Ph.D. degree. Most of the institutions that participated in the early years of this program have submitted renewal applications and all but a few of these have received continued grant support. The participating colleges and universities are providing data on the student participants at their institutions so that the Institute may evaluate the success of the program. The evaluation will help NIGMS make plans for the future of the program.

Mr. Stokes: To what extent will the Institute assume funding for the program in FY 1997?

Dr. Cassman: We intend to provide \$3 million toward the support of the Bridges to the Future Programs in FY 1997.

MARC STUDY

Mr. Stokes: What criteria was used to determine that the criteria by which to assess the program was accurate or appropriate itself?

Dr. Cassman: Prior to designing the MARC study, NIGMS convened an ad hoc panel of consultants to solicit their advice on how to evaluate the MARC program and on the types of measures that should be used. This panel was co-chaired by the directors of MARC programs at two universities. Included on the panel were other MARC program directors and faculty, other faculty involved in graduate training of minority students, experts in program evaluation, and representatives of the National Advisory General Medical Sciences Council. The panel reviewed the goals of the MARC program and historical information on funded MARC programs. The evaluation criteria were based on the review of the goals of the MARC program and the input of this panel. The advisory group met a second time to review the detailed study plans, including the evaluation criteria, before the study was conducted.

MORE PROGRAM

Mr. Stokes: I understand that the Institute is planning some new initiatives in its MORE Division, in hopes of establishing new avenues for underrepresented minorities in biomedical research. Specifically, what will this initiative allow the Institute to do to increase the representation of African Americans and other minorities in biomedical research? Please be specific.

Dr. Cassman: The Minority Opportunities in Research Division (MORE) has recently undertaken several initiatives, intended to bring to bear a variety of strategies to increase the number of underrepresented minority students pursuing careers in biomedical research. First, the MARC Honors Undergraduate Research Training (HURT) Program has been given a new name, the Undergraduate Student Training in Academic Research (U*STAR) Program and its guidelines have been revised to place more emphasis on each participating institution setting goals for increasing its production of students pursuing the Ph.D. Each institution will also be expected to evaluate its own MARC activities. This new U*STAR Program leaves intact all of the components that have characterized the MARC program since its inception, such as the selection of honor students as MARC trainees, a summer extramural research experience, and a special honors curriculum. The eligibility requirements for MARC institutions remain unchanged. One advantage of the new U*STAR Program is that it respects the heterogeneity of MARC-supported institutions, encouraging each to play to its particular strengths and be shaped by its own goals.

Complementing the U*STAR revision of the MARC Program are two other initiatives. One enables eligible MARC institutions to develop intervention strategies to reduce student attrition and improve their academic performance so that the talent pool eligible to participate as juniors and seniors in the U*STAR program is enlarged. The second initiative provides MARC-supported institutions the opportunity to develop a continual self-evaluation system and conduct an evaluation of the impact of past MARC grant support.

In the Minority Biomedical Research Support (MBRS) program, an Initiative for Minority Student Development replaces the Associate Investigator Institution category of MBRS award. Any college or university can apply. The objective of the initiative is to engage the commitment of more institutions in ameliorating the problem of underrepresentation of minorities in biomedical research. The applicants are challenged to make significant improvements in their production of underrepresented minorities who go on to biomedical research careers. Each applicant institution is expected to propose measurable objectives to achieve this, and to describe plans for evaluation. This initiative extends opportunities for the large majority of underrepresented minority students, including African-Americans, who attend institutions serving mixed populations of students. Other initiatives directed to MBRS institutions include supplements to existing awards for instrumentation, institutional enhancement and faculty workshops, as well as for strengthening existing research programs.

MBRS FUNDS TO HBCU'S

Mr. Stokes: What percentage and number of MBRS grants and funds are awarded to HBCU's?

Dr. Cassman: The number of MBRS grants awarded to HBCU's in FY 1995 was 47. This number represents 49 percent of the total MBRS grants awarded. The amount of MBRS funds awarded to HBCU's was \$19.6 million, representing 41 percent of the total MBRS funds awarded in FY 1995.

Mr. Stokes: For the record, include a listing for the FY 1980, 1985, 1990, 1993, and 1995, of MBRS grantees in rank order based on the amount and percent of total MBRS funding awarded, include the percentage figure and the amount of the award?

Dr. Cassman: The following is a listing for FY 1980, 1985, 1990, 1993, and 1995 of MBRS grantees in rank order based on amount and percent of total MBRS funding awarded.

FY 1980 MINORITY BIOMEDICAL RESEARCH SUPPORT PROGRAM

INSTITUTION	AMOUNT AWARDED	PERCENT
HOWARD UNIVERSITY	\$1,510,518	6.33%
ATLANTA UNIVERSITY CENTER	\$1,474,060	6.18%
CALIFORNIA STATE UNIVERSITY LOS ANGELES	\$969,549	4.06%
UNIVERSITY OF NEW MEXICO ALBUQUERQUE	\$914,058	3.83%
UNIVERSITY OF PUERTO RICO RIO PIEDRAS	\$898,203	3.76%
JACKSON STATE UNIVERSITY	\$782,693	3.28%
MEHARRY MEDICAL COLLEGE	\$761,683	3.19%
SOUTHERN UNIV A&M COL BATON ROUGH	\$520,181	2.18%
CHARLES R. DREW UNIVERSITY OF MED & SCI	\$514,187	2.15%
TEXAS SOUTHERN UNIVERSITY	\$458,516	1.92%
UNIVERSITY OF TEXAS EL PASO	\$456,810	1.91%
TUSKEGEE UNIVERSITY	\$433,931	1.82%
HUNTER COLLEGE	\$433,675	1.82%
CHICAGO STATE UNIVERSITY	\$380,999	1.60%
FLORIDA AGRICULTURAL AND MECHANICAL UNIV	\$363,914	1.52%
XAVIER UNIVERSITY OF LOUISIANA	\$354,346	1.48%
UNIVERSITY OF TEXAS-PAN AMERICAN	\$348,464	1.46%
NORTH CAROLINA AGRI & TECH ST UNIV	\$343,539	1.44%
ALABAMA AGRI AND MECH UNIVERSITY	\$330,642	1.39%
INCARNATE WORD COLLEGE	\$326,115	1.37%
CALIFORNIA STATE UNIV-DOMINGUEZ HILLS	\$321,262	1.35%
TENNESSEE STATE UNIVERSITY	\$321,230	1.35%
DELAWARE STATE UNIVERSITY	\$317,135	1.33%
UNIVERSITY OF CALIFORNIA SANTA CRUZ	\$304,664	1.28%
COLLEGE AT OLD WESTBURY	\$303,106	1.27%
NORTH CAROLINA CENTRAL UNIVERSITY	\$299,918	1.26%
WINSTON-SALEM STATE UNIVERSITY	\$299,553	1.26%
YORK COLLEGE	\$296,606	1.24%
NEW MEXICO STATE UNIVERSITY LAS CRUCES	\$294,362	1.23%
SAN JOSE STATE UNIVERSITY	\$291,001	1.22%
MEDGAR EVERS COLLEGE	\$277,988	1.16%
BENEDICT COLLEGE	\$259,551	1.09%
CATHOLIC UNIVERSITY OF PUERTO RICO	\$257,521	1.08%
WAYNE STATE UNIVERSITY	\$251,058	1.05%
SAVANNAH STATE COLLEGE	\$249,912	1.05%
UNIVERSITY OF TEXAS SAN ANTONIO	\$249,353	1.04%
UNIVERSITY OF MARYLAND EASTERN SHORE	\$249,194	1.04%
FISK UNIVERSITY	\$247,796	1.04%
UNIVERSITY OF HAWAII AT MANOA	\$241,561	1.01%
UNIVERSITY OF PUERTO RICO MAYAGUEZ	\$237,409	0.99%
BRONX COMMUNITY COLLEGE	\$227,109	0.95%
UNIVERSITY OF CALIFORNIA SAN DIEGO	\$224,674	0.94%
UNIVERSITY OF THE DISTRICT OF COLUMBIA	\$210,029	0.88%
TEXAS AGRICULTURAL AND IND UNIV	\$206,173	0.86%
BETHUNE-COOKMAN COLLEGE	\$202,623	0.85%

NORFOLK STATE UNIVERSITY	\$199,890	0.84%
PRAIRIE VIEW AGRI & MECH UNIVERSITY	\$196,166	0.82%
JOHNSON C. SMITH UNIVERSITY	\$194,990	0.82%
CITY COLLEGE OF NEW YORK	\$191,640	0.80%
NORTHEASTERN OKLAHOMA STATE UNIVERSITY	\$191,094	0.80%
COLLEGE OF SANTA FE	\$183,035	0.77%
VIRGINIA STATE UNIVERSITY	\$182,909	0.77%
NEW MEXICO HIGHLANDS UNIVERSITY	\$178,549	0.75%
TALLADEGA COLLEGE	\$178,273	0.75%
ALCORN STATE UNIVERSITY	\$175,028	0.73%
SOUTHEASTERN OKLAHOMA STATE UNIVERSITY	\$167,986	0.70%
DILLARD UNIVERSITY	\$166,956	0.70%
LEMOYNE-OWEN COLLEGE	\$152,726	0.64%
UNIVERSITY OF ALBUQUERQUE	\$144,474	0.61%
LINCOLN UNIVERSITY	\$144,188	0.60%
SELMA UNIVERSITY	\$144,103	0.60%
LONG ISLAND UNIVERSITY BROOKLYN CENTER	\$129,453	0.54%
STILLMAN COLLEGE	\$128,214	0.54%
TOUGALOO COLLEGE	\$127,641	0.53%
CENTRAL STATE UNIV (WILBERFORCE, OH)	\$124,896	0.52%
MISSISSIPPI INDUSTRIAL COLLEGE	\$122,720	0.51%
BISHOP COLLEGE	\$120,760	0.51%
SOUTH CAROLINA STATE COLLEGE	\$119,809	0.50%
VOORHEES COLLEGE	\$118,952	0.50%
EAST LOS ANGELES COLLEGE	\$118,430	0.50%
KNOXVILLE COLLEGE	\$110,066	0.46%
INTER AMERICAN UNIVERSITY OF PUERTO RICO	\$107,260	0.45%
KENTUCKY STATE UNIVERSITY	\$106,779	0.45%
ELIZABETH CITY STATE UNIVERSITY	\$100,085	0.42%
FORT VALLEY STATE COLLEGE	\$91,052	0.38%
MILES COLLEGE	\$74,861	0.31%
GRAMBLING STATE UNIVERSITY	\$71,810	0.30%
NAVAJO COMMUNITY COLLEGE SHIPROCK	\$53,301	0.22%
UNIVERSITY OF HAWAII AT HILO	\$28,480	0.12%
ALBANY STATE COLLEGE	\$5,275	0.02%
TOTAL	\$23,868,722	100.00%

FY 1985 MINORITY BIOMEDICAL RESEARCH SUPPORT PROGRAM

INSTITUTION	AMOUNT	
	AWARDED	PERCENT
HOWARD UNIVERSITY	\$2,297,424	6.45%
UNIVERSITY OF PUERTO RICO RIO PIEDRAS	\$1,751,027	4.92%
ATLANTA UNIVERSITY CENTER	\$1,626,440	4.57%
CALIFORNIA STATE UNIVERSITY LOS ANGELES	\$1,574,064	4.42%
MEHARRY MEDICAL COLLEGE	\$923,539	2.59%
UNIVERSITY OF NEW MEXICO ALBUQUERQUE	\$860,757	2.42%
JACKSON STATE UNIVERSITY	\$744,178	2.09%
TUSKEGEE UNIVERSITY	\$713,043	2.00%
UNIVERSITY OF TEXAS SAN ANTONIO	\$682,473	1.92%
CHICAGO STATE UNIVERSITY	\$662,470	1.86%
UNIVERSITY OF PUERTO RICO MED SCIENCES	\$656,642	1.84%
FLORIDA AGRICULTURAL AND MECHANICAL UNIV	\$645,655	1.81%
TENNESSEE STATE UNIVERSITY	\$632,045	1.77%
CITY COLLEGE OF NEW YORK	\$620,673	1.74%
WAYNE STATE UNIVERSITY	\$590,812	1.66%
XAVIER UNIVERSITY OF LOUISIANA	\$564,720	1.59%
BENEDICT COLLEGE	\$536,666	1.51%
INCARNATE WORD COLLEGE	\$522,645	1.47%
COLLEGE AT OLD WESTBURY	\$512,828	1.44%
UNIVERSITY OF TEXAS EL PASO	\$497,166	1.40%
BRONX COMMUNITY COLLEGE	\$497,160	1.40%
FAYETTEVILLE STATE UNIVERSITY	\$470,623	1.32%
HUNTER COLLEGE	\$451,123	1.27%
NORTH CAROLINA CENTRAL UNIVERSITY	\$444,471	1.25%
UNIVERSITY OF PUERTO RICO MAYAGUEZ	\$437,052	1.23%
YORK COLLEGE	\$421,467	1.18%
UNIVERSITY OF THE DISTRICT OF COLUMBIA	\$412,204	1.16%
MEHARRY MEDICAL COLLEGE	\$411,482	1.16%
NEW MEXICO STATE UNIVERSITY LAS CRUCES	\$369,221	1.04%
UNIVERSITY OF PUERTO RICO RIO PIEDRAS	\$362,032	1.02%
UNIVERSITY OF SOUTHERN COLORADO	\$357,457	1.00%
BETHUNE-COOKMAN COLLEGE	\$355,438	1.00%
SAVANNAH STATE COLLEGE	\$354,591	1.00%
SOUTHERN UNIV A&M COL BATON ROUGH	\$353,942	0.99%
RUTGERS THE STATE UNIV NEW BRUNSWICK	\$338,718	0.95%
INTER AMERICAN UNIVERSITY OF PUERTO RICO	\$336,348	0.94%
UNIVERSITY OF HAWAII AT MANOA	\$335,390	0.94%
CATHOLIC UNIVERSITY OF PUERTO RICO	\$332,194	0.93%
TUSKEGEE UNIVERSITY	\$326,477	0.92%
SAN JOSE STATE UNIVERSITY	\$326,364	0.92%
TEXAS SOUTHERN UNIVERSITY	\$323,826	0.91%
UNIVERSITY OF CALIFORNIA SANTA CRUZ	\$314,801	0.88%
SELMA UNIVERSITY	\$297,281	0.83%
FLORIDA INTERNATIONAL UNIVERSITY	\$296,463	0.83%

MONTANA STATE UNIVERSITY	\$291,788	0.82%
CALIFORNIA STATE UNIV-DOMINGUEZ HILLS	\$286,555	0.80%
WINSTON-SALEM STATE UNIVERSITY	\$284,123	0.80%
UNIVERSITY OF HAWAII AT HILO	\$276,161	0.78%
UNIVERSITY OF TEXAS-PAN AMERICAN	\$259,181	0.73%
UNIVERSITY OF CALIFORNIA SAN DIEGO	\$258,408	0.73%
TOUGALOO COLLEGE	\$256,110	0.72%
FLORIDA AGRICULTURAL AND MECHANICAL UNIV	\$252,543	0.71%
MEDGAR EVERS COLLEGE	\$248,307	0.70%
PAINE COLLEGE	\$240,269	0.67%
HERBERT H. LEHMAN COLLEGE	\$236,837	0.67%
SPELMAN COLLEGE	\$236,492	0.66%
FISK UNIVERSITY	\$235,405	0.66%
NORFOLK STATE UNIVERSITY	\$233,561	0.66%
DILLARD UNIVERSITY	\$231,419	0.65%
ALABAMA STATE UNIVERSITY	\$226,036	0.63%
VIRGINIA STATE UNIVERSITY	\$224,084	0.63%
NORTH CAROLINA AGRI & TECH ST UNIV	\$222,767	0.63%
FOND DU LAC RESERVATION BUSINESS COMM	\$219,991	0.62%
TEXAS AGRICULTURAL AND IND UNIV	\$218,572	0.61%
LINCOLN UNIVERSITY	\$204,688	0.57%
PRAIRIE VIEW AGRI & MECH UNIVERSITY	\$204,457	0.57%
DELAWARE STATE UNIVERSITY	\$200,075	0.56%
HUMACAO UNIVERSITY COLLEGE	\$192,728	0.54%
CLARK ATLANTA UNIVERSITY	\$192,019	0.54%
CENTRAL STATE UNIV (WILBERFORCE, OH)	\$190,836	0.54%
SOUTHEASTERN OKLAHOMA STATE UNIVERSITY	\$185,727	0.52%
NEW MEXICO HIGHLANDS UNIVERSITY	\$179,910	0.51%
JOHNSON C. SMITH UNIVERSITY	\$174,034	0.49%
SOUTHERN UNIV A&M COL NEW ORLEANS	\$169,465	0.48%
ALBANY STATE COLLEGE	\$166,468	0.47%
UNIVERSITY OF THE VIRGIN ISLANDS	\$156,211	0.44%
LINCOLN UNIVERSITY	\$147,984	0.42%
CAYEY UNIVERSITY COLLEGE	\$145,435	0.41%
EAST LOS ANGELES COLLEGE	\$144,915	0.41%
UNIVERSITY OF ARKANSAS AT PINE BLUFF	\$131,944	0.37%
KENTUCKY STATE UNIVERSITY	\$129,833	0.36%
NORTHERN ARIZONA UNIVERSITY	\$127,167	0.36%
COPPIN STATE COLLEGE	\$125,164	0.35%
TALLADEGA COLLEGE	\$122,879	0.35%
BENNETT COLLEGE	\$119,049	0.33%
NAVAJO COMMUNITY COLLEGE SHIPROCK	\$106,838	0.30%
SHAW UNIVERSITY	\$104,112	0.29%
BISHOP COLLEGE	\$100,646	0.28%
SOUTH CAROLINA STATE COLLEGE	\$95,773	0.27%
SOUTHERN UNIVERSITY SHREVEPORT-BOSSIER	\$80,198	0.23%
RUST COLLEGE	\$77,620	0.22%
LEMOYNE-OWEN COLLEGE	\$58,514	0.16%
COLLEGE OF SANTA FE	\$57,439	0.16%
MISSISSIPPI VALLEY STATE UNIVERSITY	\$29,793	0.08%
ST. MARY'S UNIVERSITY	\$12,587	0.04%
TOTAL	\$35,614,509	100.00%

FY 1990 MINORITY BIOMEDICAL RESEARCH SUPPORT GRANTS

INSTITUTION	AMOUNT AWARDED	PERCENT
UNIVERSITY OF PUERTO RICO RIO PIEDRAS	\$1,459,577	3.60%
HOWARD UNIVERSITY	\$1,457,274	3.59%
CALIFORNIA STATE UNIVERSITY LOS ANGELES	\$1,098,502	2.71%
MOREHOUSE SCHOOL OF MEDICINE	\$1,043,532	2.57%
MEHARRY MEDICAL COLLEGE	\$998,684	2.46%
UNIVERSITY OF PUERTO RICO MED SCIENCES	\$989,293	2.44%
FLORIDA AGRICULTURAL AND MECHANICAL UNIV	\$942,202	2.32%
ATLANTA UNIVERSITY CENTER	\$922,279	2.27%
CITY COLLEGE OF NEW YORK	\$897,093	2.21%
MOREHOUSE COLLEGE	\$850,761	2.10%
TUSKEGEE UNIVERSITY	\$827,741	2.04%
MEHARRY MEDICAL COLLEGE	\$773,893	1.91%
WAYNE STATE UNIVERSITY	\$767,196	1.89%
PAN AMERICAN UNIVERSITY	\$687,856	1.70%
CHICAGO STATE UNIVERSITY	\$651,077	1.60%
UNIVERSITY OF TEXAS SAN ANTONIO	\$633,276	1.56%
CLARK ATLANTA UNIVERSITY	\$628,354	1.55%
TENNESSEE STATE UNIVERSITY	\$623,382	1.54%
PONCE SCHOOL OF MEDICINE	\$616,398	1.52%
YORK COLLEGE	\$595,344	1.47%
UNIVERSITY OF TEXAS EL PASO	\$587,824	1.45%
HUNTER COLLEGE	\$579,413	1.43%
SAN JOSE STATE UNIVERSITY	\$577,910	1.42%
UNIVERSITY OF NEW MEXICO ALBUQUERQUE	\$573,776	1.41%
TEXAS SOUTHERN UNIVERSITY	\$566,392	1.40%
JACKSON STATE UNIVERSITY	\$563,816	1.39%
BETHUNE-COOKMAN COLLEGE	\$549,683	1.35%
XAVIER UNIVERSITY OF LOUISIANA	\$510,556	1.26%
UNIVERSITY OF CALIFORNIA SANTA CRUZ	\$507,158	1.25%
BENEDICT COLLEGE	\$497,346	1.23%
WINSTON-SALEM STATE UNIVERSITY	\$485,213	1.20%
COLLEGE AT OLD WESTBURY	\$480,859	1.19%
UNIVERSITY OF HAWAII AT HILO	\$459,519	1.13%
NORTH CAROLINA AGRI & TECH ST UNIV	\$455,105	1.12%
NEW MEXICO HIGHLANDS UNIVERSITY	\$454,637	1.12%
HAMPTON UNIVERSITY	\$432,592	1.07%
UNIVERSITY OF PUERTO RICO MAYAGUEZ	\$423,356	1.04%
SOUTHERN UNIV A&M COL BATON ROUGE	\$422,601	1.04%
HUMACAO UNIVERSITY COLLEGE	\$403,259	0.99%
UNIVERSITY OF ARKANSAS AT PINE BLUFF	\$401,471	0.99%
MONTANA STATE UNIVERSITY	\$394,287	0.97%
DELAWARE STATE COLLEGE	\$389,066	0.96%
UNIVERSITY OF THE DISTRICT OF COLUMBIA	\$380,008	0.94%
NEW MEXICO STATE UNIVERSITY LAS CRUCES	\$378,980	0.93%
UNIVERSITY OF SOUTHERN COLORADO	\$378,186	0.93%
SELMA UNIVERSITY	\$363,652	0.90%

HERBERT H. LEHMAN COLLEGE	\$363,556	0.90%
CALIFORNIA STATE UNIVERSITY LONG BEACH	\$349,997	0.86%
JOHNSON C. SMITH UNIVERSITY	\$343,542	0.85%
BRONX COMMUNITY COLLEGE	\$338,667	0.83%
UNIVERSITY OF HAWAII AT MANOA	\$336,721	0.83%
LOS ANGELES COMMUNITY COLLEGE DISTRICT	\$321,219	0.79%
MEDGAR EVERS COLLEGE	\$318,627	0.79%
NORTHERN ARIZONA UNIVERSITY	\$316,898	0.78%
FLORIDA INTERNATIONAL UNIVERSITY	\$313,765	0.77%
RUTGERS THE STATE UNIV NEWARK	\$301,248	0.74%
ALABAMA STATE UNIVERSITY	\$280,627	0.69%
FAYETTEVILLE STATE UNIVERSITY	\$277,184	0.68%
PRAIRIE VIEW AGRI & MECH UNIVERSITY	\$276,128	0.68%
TEXAS WOMAN'S UNIVERSITY	\$243,351	0.60%
TOUGALOO COLLEGE	\$240,759	0.59%
FISK UNIVERSITY	\$238,426	0.59%
NORFOLK STATE UNIVERSITY	\$237,392	0.59%
UNIVERSITY OF THE VIRGIN ISLANDS	\$225,548	0.56%
TEXAS AGRICULTURAL AND IND UNIV	\$222,673	0.55%
UNIVERSITY OF GUAM	\$210,915	0.52%
CAYEY UNIVERSITY COLLEGE	\$206,894	0.51%
BENNETT COLLEGE	\$205,722	0.51%
LINCOLN UNIVERSITY	\$205,655	0.51%
MOUNT ST. MARY'S COLLEGE	\$205,313	0.51%
COPPIN STATE COLLEGE	\$199,525	0.49%
ALBANY STATE COLLEGE	\$199,196	0.49%
VIRGINIA STATE UNIVERSITY	\$198,589	0.49%
ST. MARY'S UNIVERSITY	\$192,630	0.47%
CALIFORNIA STATE UNIV-DOMINGUEZ HILLS	\$174,893	0.43%
LINCOLN UNIVERSITY	\$167,622	0.41%
CHARLES R. DREW UNIVERSITY OF MED & SCI	\$166,122	0.41%
STILLMAN COLLEGE	\$165,814	0.41%
NORTH CAROLINA CENTRAL UNIVERSITY	\$161,672	0.40%
SOUTHEASTERN OKLAHOMA STATE UNIVERSITY	\$157,986	0.39%
ALCORN STATE UNIVERSITY	\$153,620	0.38%
SOUTH CAROLINA STATE COLLEGE	\$149,185	0.37%
ALABAMA AGRI AND MECH UNIVERSITY	\$148,471	0.37%
FOND DU LAC RESERVATION BUSINESS COMM	\$147,862	0.36%
SOUTHERN UNIV A&M COL SHREVEPORT-BOSSIER	\$143,321	0.35%
CLARK ATLANTA UNIVERSITY	\$142,171	0.35%
CATHOLIC UNIVERSITY OF PUERTO RICO	\$141,013	0.35%
KENTUCKY STATE UNIVERSITY	\$138,421	0.34%
GRAMBLING STATE UNIVERSITY	\$137,377	0.34%
INTER AMERICAN UNIVERSITY OF PUERTO RICO	\$128,721	0.32%
PHILANDER SMITH COLLEGE	\$128,548	0.32%
RUST COLLEGE	\$121,030	0.30%
SPELMAN COLLEGE	\$120,918	0.30%
NAVAJO COMMUNITY COLLEGE SHIPROCK	\$119,906	0.30%
CALIFORNIA STATE UNIVERSITY FULLERTON	\$118,022	0.29%
SOUTHERN UNIV A&M COL NEW ORLEANS	\$98,465	0.24%

COLLEGE OF SANTA FE	\$88,868	0.22%
LANE COLLEGE	\$69,269	0.17%
UNIVERSITY OF PUERTO RICO SAN JUAN	\$59,533	0.15%
SAN JOSE STATE UNIVERSITY	\$55,128	0.14%
TALLADEGA COLLEGE	\$53,995	0.13%
UNIVERSITY OF CALIFORNIA SAN DIEGO	\$47,483	0.12%
PENNSYLVANIA STATE UNIVERSITY	\$18,049	0.04%
TOTAL	<u>\$40,574,631</u>	100.00%

FY 1993 MINORITY BIOMEDICAL RESEARCH SUPPORT GRANTS

INSTITUTION	AMOUNT AWARDED	PERCENT
MOREHOUSE SCHOOL OF MEDICINE	\$1,530,447	3.40%
CALIFORNIA STATE UNIVERSITY LOS ANGELES	\$1,504,455	3.34%
UNIVERSITY OF PUERTO RICO RIO PIEDRAS	\$1,235,387	2.74%
HOWARD UNIVERSITY	\$1,214,865	2.70%
MEHARRY MEDICAL COLLEGE	\$1,143,995	2.54%
HOWARD UNIVERSITY MEDICAL SCHOOL	\$1,073,096	2.38%
CITY COLLEGE OF NEW YORK	\$1,035,498	2.30%
UNIVERSITY OF PUERTO RICO MED SCIENCES	\$994,010	2.21%
CHICAGO STATE UNIVERSITY	\$940,788	2.09%
SAN JOSE STATE UNIVERSITY	\$914,194	2.03%
YORK COLLEGE	\$904,957	2.01%
UNIVERSITY OF TEXAS SAN ANTONIO	\$884,906	1.96%
UNIVERSITY OF TEXAS EL PASO	\$862,010	1.91%
MOREHOUSE COLLEGE	\$834,093	1.85%
UNIVERSITY OF TEXAS-PAN AMERICAN	\$798,949	1.77%
WAYNE STATE UNIVERSITY	\$797,238	1.77%
CLARK ATLANTA UNIVERSITY	\$769,543	1.71%
NEW MEXICO STATE UNIVERSITY LAS CRUCES	\$727,943	1.62%
PONCE SCHOOL OF MEDICINE	\$692,307	1.54%
FLORIDA AGRICULTURAL AND MECHANICAL UNIV	\$659,315	1.46%
HERBERT H. LEHMAN COLLEGE	\$657,946	1.46%
TUSKEGEE UNIVERSITY	\$643,617	1.43%
CALIFORNIA STATE UNIVERSITY LONG BEACH	\$591,304	1.31%
JACKSON STATE UNIVERSITY	\$590,546	1.31%
RUTGERS THE STATE UNIV NEW BRUNSWICK	\$590,236	1.31%
UNIVERSITY OF CALIFORNIA SANTA CRUZ	\$580,314	1.29%
XAVIER UNIVERSITY OF LOUISIANA	\$574,223	1.27%
FLORIDA INTERNATIONAL UNIVERSITY	\$538,050	1.19%
SPELMAN COLLEGE	\$536,383	1.19%
PRAIRIE VIEW AGRI & MECH UNIVERSITY	\$534,530	1.19%
HUNTER COLLEGE	\$528,682	1.17%
WINSTON-SALEM STATE UNIVERSITY	\$495,375	1.10%
CHARLES R. DREW UNIVERSITY OF MED & SCI	\$471,268	1.05%
UNIVERSITY OF ARKANSAS AT PINE BLUFF	\$468,778	1.04%
UNIVERSITY OF PUERTO RICO MAYAGUEZ	\$466,877	1.04%
JOHNSON C. SMITH UNIVERSITY	\$464,495	1.03%
COLLEGE AT OLD WESTBURY	\$442,892	0.98%
BENEDICT COLLEGE	\$440,619	0.98%
CALIFORNIA STATE UNIVERSITY NORTHRIDGE	\$440,041	0.98%
GRAMBLING STATE UNIVERSITY	\$437,082	0.97%
DELAWARE STATE UNIVERSITY	\$431,962	0.96%
HUMACAO UNIVERSITY COLLEGE	\$427,526	0.95%
UNIVERSITY OF NEW MEXICO ALBUQUERQUE	\$422,295	0.94%
TEXAS SOUTHERN UNIVERSITY	\$415,473	0.92%

UNIVERSITY OF SOUTHERN COLORADO	\$397,914	0.88%
UNIVERSITY OF GUAM	\$382,671	0.85%
UNIVERSITY OF THE DISTRICT OF COLUMBIA	\$382,166	0.85%
EAST LOS ANGELES COLLEGE	\$368,600	0.82%
CALIFORNIA STATE UNIVERSITY HAYWARD	\$363,872	0.81%
UNIVERSITY OF THE VIRGIN ISLANDS	\$344,711	0.76%
FISK UNIVERSITY	\$342,992	0.76%
UNIVERSITY OF CALIFORNIA SAN DIEGO	\$327,679	0.73%
CALIFORNIA STATE UNIVERSITY FULLERTON	\$327,636	0.73%
SAN DIEGO STATE UNIVERSITY	\$324,122	0.72%
BARRY UNIVERSITY	\$321,008	0.71%
BRONX COMMUNITY COLLEGE	\$318,049	0.71%
ST. MARY'S UNIVERSITY	\$314,083	0.70%
SOUTHEASTERN OKLAHOMA STATE UNIVERSITY	\$311,774	0.69%
SOUTHERN UNIV A&M COL BATON ROUGE	\$309,495	0.69%
CALIFORNIA STATE UNIV-DOMINGUEZ HILLS	\$306,651	0.68%
UNIVERSITY OF HAWAII AT MANOA	\$302,784	0.67%
CHAMINADE UNIVERSITY OF HONOLULU	\$296,371	0.66%
ALABAMA AGRI AND MECH UNIVERSITY	\$295,046	0.65%
LINCOLN UNIVERSITY	\$287,897	0.64%
BETHUNE-COOKMAN COLLEGE	\$276,722	0.61%
FAYETTEVILLE STATE UNIVERSITY	\$273,662	0.61%
TEXAS WOMAN'S UNIVERSITY	\$271,770	0.60%
UNIVERSITY OF HAWAII AT HILO	\$266,898	0.59%
INTER AMERICAN UNIVERSITY OF PUERTO RICO	\$258,973	0.57%
SELMA UNIVERSITY	\$257,705	0.57%
BENNETT COLLEGE	\$251,840	0.56%
NEW MEXICO HIGHLANDS UNIVERSITY	\$251,257	0.56%
COPPIN STATE COLLEGE	\$250,162	0.56%
OAKWOOD COLLEGE	\$245,603	0.54%
ALABAMA STATE UNIVERSITY	\$243,858	0.54%
TEXAS A&M UNIVERSITY-KINGSVILLE	\$243,100	0.54%
TOUGALOO COLLEGE	\$241,604	0.54%
ALBANY STATE COLLEGE	\$238,025	0.53%
TALLADEGA COLLEGE	\$231,588	0.51%
MONTANA STATE UNIVERSITY	\$229,090	0.51%
NAVAJO COMMUNITY COLLEGE SHIPROCK	\$228,734	0.51%
VIRGINIA STATE UNIVERSITY	\$218,441	0.48%
STILLMAN COLLEGE	\$203,340	0.45%
NORTH CAROLINA AGRI & TECH ST UNIV	\$201,850	0.45%
KENTUCKY STATE UNIVERSITY	\$194,419	0.43%
SOUTH CAROLINA STATE COLLEGE	\$182,049	0.40%
ALCORN STATE UNIVERSITY	\$176,787	0.39%
CAYEY UNIVERSITY COLLEGE	\$150,028	0.33%
SOUTHERN UNIVERSITY SHREVEPORT-BOSSIER	\$149,009	0.33%
PHILANDER SMITH COLLEGE	\$148,924	0.33%
JARVIS CHRISTIAN COLLEGE	\$137,532	0.31%
ELIZABETH CITY STATE UNIVERSITY	\$132,415	0.29%

RUST COLLEGE	\$119,612	0.27%
FOND DU LAC RESERVATION BUSINESS COMM	\$119,486	0.27%
NORFOLK STATE UNIVERSITY	\$98,077	0.22%
INCARNATE WORD COLLEGE	\$90,316	0.20%
LANE COLLEGE	\$83,748	0.19%
MORRIS COLLEGE	\$66,212	0.15%
TOTAL	<u>\$45,066,867</u>	100.00%

FY 1995 MINORITY BIOMEDICAL RESEARCH SUPPORT GRANTS

INSTITUTION	AMOUNT	
	AWARDED	PERCENT
CALIFORNIA STATE UNIVERSITY LOS ANGELES	\$1,937,419	4.07%
UNIVERSITY OF PUERTO RICO RIO PIEDRAS	\$1,753,109	3.68%
MEHARRY MEDICAL COLLEGE	\$1,396,880	2.93%
HOWARD UNIVERSITY	\$1,332,180	2.80%
CALIFORNIA STATE UNIVERSITY NORTHRIDGE	\$1,200,913	2.52%
PONCE SCHOOL OF MEDICINE	\$1,130,660	2.37%
WAYNE STATE UNIVERSITY	\$1,104,291	2.32%
UNIVERSITY OF TEXAS SAN ANTONIO	\$1,097,277	2.30%
UNIVERSITY OF PUERTO RICO MED SCIENCES	\$1,093,100	2.29%
CLARK ATLANTA UNIVERSITY	\$1,069,115	2.24%
MORGAN STATE UNIVERSITY	\$930,589	1.95%
FLORIDA AGRICULTURAL AND MECHANICAL UNIV	\$928,894	1.95%
MOREHOUSE SCHOOL OF MEDICINE	\$903,981	1.90%
YORK COLLEGE	\$866,815	1.82%
UNIVERSITY OF NEW MEXICO ALBUQUERQUE	\$854,713	1.79%
TEXAS SOUTHERN UNIVERSITY	\$842,389	1.77%
NEW MEXICO STATE UNIVERSITY LAS CRUCES	\$832,660	1.75%
UNIVERSITY OF PUERTO RICO MAYAGUEZ	\$795,824	1.67%
CALIFORNIA STATE UNIVERSITY HAYWARD	\$759,108	1.59%
NORTH CAROLINA CENTRAL UNIVERSITY	\$747,582	1.57%
BARRY UNIVERSITY	\$694,686	1.46%
MOREHOUSE COLLEGE	\$665,647	1.40%
CHICAGO STATE UNIVERSITY	\$661,719	1.39%
FLORIDA INTERNATIONAL UNIVERSITY	\$651,062	1.37%
UNIVERSITY OF HAWAII AT HILO	\$642,852	1.35%
UNIVERSITY OF TEXAS-PAN AMERICAN	\$633,335	1.33%
UNIVERSITY OF TEXAS EL PASO	\$628,434	1.32%
CALIFORNIA STATE UNIVERSITY LONG BEACH	\$596,486	1.25%
UNIVERSITY OF CALIFORNIA SAN DIEGO	\$596,177	1.25%
JACKSON STATE UNIVERSITY	\$543,405	1.14%
CALIFORNIA STATE UNIV-DOMINGUEZ HILLS	\$542,977	1.14%
TUSKEGEE UNIVERSITY	\$529,774	1.11%
UNIVERSITY OF ARKANSAS AT PINE BLUFF	\$518,399	1.09%
SAN DIEGO STATE UNIVERSITY	\$509,322	1.07%
UNIVERSITY OF GUAM	\$509,290	1.07%
FAYETTEVILLE STATE UNIVERSITY	\$508,435	1.07%
HERBERT H. LEHMAN COLLEGE	\$494,221	1.04%
WINSTON-SALEM STATE UNIVERSITY	\$493,315	1.04%
TEXAS WOMAN'S UNIVERSITY	\$492,854	1.03%
SAN FRANCISCO STATE UNIVERSITY	\$482,772	1.01%
HUMACAO UNIVERSITY COLLEGE	\$449,357	0.94%
UNIVERSITY OF SOUTHERN COLORADO	\$446,848	0.94%
CALIFORNIA STATE UNIVERSITY FULLERTON	\$410,810	0.86%
HUNTER COLLEGE	\$406,396	0.85%
CHARLES R. DREW UNIVERSITY OF MED & SCI	\$405,739	0.85%
UNIVERSITY OF THE VIRGIN ISLANDS	\$402,245	0.84%
XAVIER UNIVERSITY OF LOUISIANA	\$397,140	0.83%

CENTRAL UNIVERSITY OF THE CARIBE	\$394,633	0.83%
ALABAMA STATE UNIVERSITY	\$381,120	0.80%
CAYEY UNIVERSITY COLLEGE	\$379,023	0.80%
BENNETT COLLEGE	\$376,256	0.79%
UNIVERSITY OF CALIFORNIA SANTA CRUZ	\$362,866	0.76%
BRONX COMMUNITY COLLEGE	\$356,430	0.75%
CITY COLLEGE OF NEW YORK	\$354,230	0.74%
ST. JOHN'S UNIVERSITY	\$352,064	0.74%
EAST LOS ANGELES COLLEGE	\$324,327	0.68%
BETHUNE-COOKMAN COLLEGE	\$319,636	0.67%
COLLEGE AT OLD WESTBURY	\$302,658	0.64%
VIRGINIA STATE UNIVERSITY	\$299,494	0.63%
PRAIRIE VIEW AGRI & MECH UNIVERSITY	\$297,108	0.62%
ST. PAUL'S COLLEGE	\$296,778	0.62%
MONTANA STATE UNIVERSITY	\$293,911	0.62%
LINCOLN UNIVERSITY	\$283,393	0.59%
BENEDICT COLLEGE	\$278,723	0.58%
JOHNSON C. SMITH UNIVERSITY	\$267,519	0.56%
INTER AMERICAN UNIVERSITY OF PUERTO RICO	\$262,103	0.55%
OAKWOOD COLLEGE	\$260,928	0.55%
SPELMAN COLLEGE	\$256,711	0.54%
STILLMAN COLLEGE	\$252,802	0.53%
RUTGERS THE STATE UNIV NEWARK	\$251,610	0.53%
NEW MEXICO HIGHLANDS UNIVERSITY	\$250,944	0.53%
ALCORN STATE UNIVERSITY	\$241,061	0.51%
TOUGALOO COLLEGE	\$222,423	0.47%
UNIVERSITY OF HAWAII AT MANOA	\$218,082	0.46%
UNIVERSITY OF THE DISTRICT OF COLUMBIA	\$211,844	0.44%
TENNESSEE STATE UNIVERSITY	\$206,349	0.43%
FISK UNIVERSITY	\$200,691	0.42%
RUST COLLEGE	\$199,878	0.42%
COPPIN STATE COLLEGE	\$197,773	0.42%
KENTUCKY STATE UNIVERSITY	\$196,187	0.41%
TALLADEGA COLLEGE	\$186,309	0.39%
DELAWARE STATE UNIVERSITY	\$176,747	0.37%
ELIZABETH CITY STATE UNIVERSITY	\$175,210	0.37%
SPELMAN COLLEGE	\$167,519	0.35%
PHILANDER SMITH COLLEGE	\$159,117	0.33%
GRAMBLING STATE UNIVERSITY	\$152,230	0.32%
NAVAJO COMMUNITY COLLEGE SHIPROCK	\$148,130	0.31%
NORFOLK STATE UNIVERSITY	\$145,691	0.31%
SOUTHEASTERN OKLAHOMA STATE UNIVERSITY	\$127,620	0.27%
JARVIS CHRISTIAN COLLEGE	\$124,768	0.26%
ST. MARY'S UNIVERSITY	\$117,872	0.25%
NORFOLK STATE UNIVERSITY	\$116,672	0.24%
SPELMAN COLLEGE	\$116,622	0.24%
TEXAS A&M UNIVERSITY-KINGSVILLE	\$116,611	0.24%
NORTHERN ARIZONA UNIVERSITY	\$104,329	0.22%
SELMA UNIVERSITY	\$89,166	0.19%
SAN JOSE STATE UNIVERSITY	\$80,327	0.17%
ALBANY STATE COLLEGE	\$76,765	0.16%
SOUTHERN UNIV A&M COL BATON ROUGE	\$10,000	0.02%
DELAWARE STATE UNIVERSITY	\$10,000	0.02%
UNIVERSITY OF TEXAS-PAN AMERICAN	\$10,000	0.02%
TOTAL	\$47,652,456	100.0%

"BETTER" AND "SMALL" INSTITUTIONS

Mr. Stokes: During your response to the \$1.5 million ceiling question, you referenced two categories of institutions-- "better institutions" and "small institutions." For each of these categories, would you provide a description, a profile, and a listing of the institutions which you place in each of these categories?

Dr. Cassman: A number of the institutions that receive MBRS support are research-oriented. Not unexpectedly, most of these same institutions offer the Ph.D. degree. One objective of the MBRS Program has been to provide support sufficient to help faculty at these institutions who are engaged in research to become competitive for regular NIH funding. In fiscal year 1995, the average annual direct costs awarded to an MBRS-supported investigator at such an institution was \$60,789. This amount is less than NIH provides to most grantees, including the FIRST Award, (\$75,000 per year), an award to help new investigators launch their research careers. Lifting the cap should make it possible to provide sufficient funds to MBRS investigators to give them the opportunity to develop competitive research programs. We recognize the value of the small schools supported by MBRS, most of which focus on undergraduate education, some of which also grant the Masters degree. While it is often challenging for these institutions to mount a substantial research program, they do play a valuable role in exposing students and faculty to research, and they do produce students who go on to pursue advanced degrees in the biomedical sciences.

Lists of institutions in these "categories" that were funded in fiscal year 1995 are presented below:

Research-oriented MBRS Institutions:

California State University-Los Angeles
 Charles R. Drew Medical School
 Florida Agricultural and Mechanical University
 Howard University
 Jackson State University
 Meharry Medical College
 Morehouse School of Medicine
 Ponce School of Medicine
 University of Puerto Rico Medical Sciences
 University of Puerto Rico-Rio Piedras
 University of Texas-El Paso
 University of Texas-San Antonio

Community Colleges, Bachelors and Masters Degree Granting MBRS Institutions:

Alabama State University
 Albany State College
 Barry University
 Benedict College.

Bethune-Cookman College
 Bronx Community College
 California State University-Dominguez Hills
 California State University-Hayward
 California State University-Northridge
 Cayey University College
 Chicago State University
 Clark Atlanta University
 College at Old Westbury
 Delaware State University
 East Los Angeles College
 Fayetteville State University
 Fisk University
 Florida International University
 Herbert H. Lehman College
 Humacao University College
 Inter-American University of Puerto Rico
 Johnson C. Smith University
 Lincoln University
 Morehouse College
 Morgan State University
 Navajo Community College-Shiprock
 New Mexico Highlands University
 Norfolk State University
 North Carolina Central University
 Prairie View Agricultural and Mechanical University
 San Francisco State University
 San Jose State University
 Selma University
 Southern University Agricultural and Mechanical College-Baton Rouge
 Spelman College
 Tennessee State University
 Texas Southern University
 Tougaloo College
 Tuskegee University
 University of Arkansas at Pine Bluff
 University Central del Caribe
 University of Guam
 University of Hawaii at Hilo
 University of Puerto Rico-Mayaguez
 University of Southern Colorado
 University of Texas-Pan American
 University of the District of Columbia
 University of the Virgin Islands
 Xavier University of Louisiana
 York College

RESEARCH TRAINING

Mr. Stokes: Please provide for the record, the Institute's statistics on the number of individuals who receive support through the Institute's regular research training grants? How many minorities receive support through the Institute's regular training program?

Dr. Cassman: The Institute's predoctoral training grant programs supported 3,085 graduate students in 1994, with 1,149 being new appointments. For the first time, the appointment form for new trainees asked about the individual's race/ethnicity. The response rate to this question was 83%. About 8% of the new appointments that responded to this question were from underrepresented minority groups, i.e., Black, Hispanic, Pacific Islander, or American Indian/Alaskan Native. This represents 79 individuals. In the Institute's much smaller postdoctoral programs, 13% or 6 trainees were from these same underrepresented minority groups.

Mr. Stokes: To what extent have either of these numbers increased or decreased since 1993?

Dr. Cassman: Trainees were not asked about race/ethnicity prior to 1994.

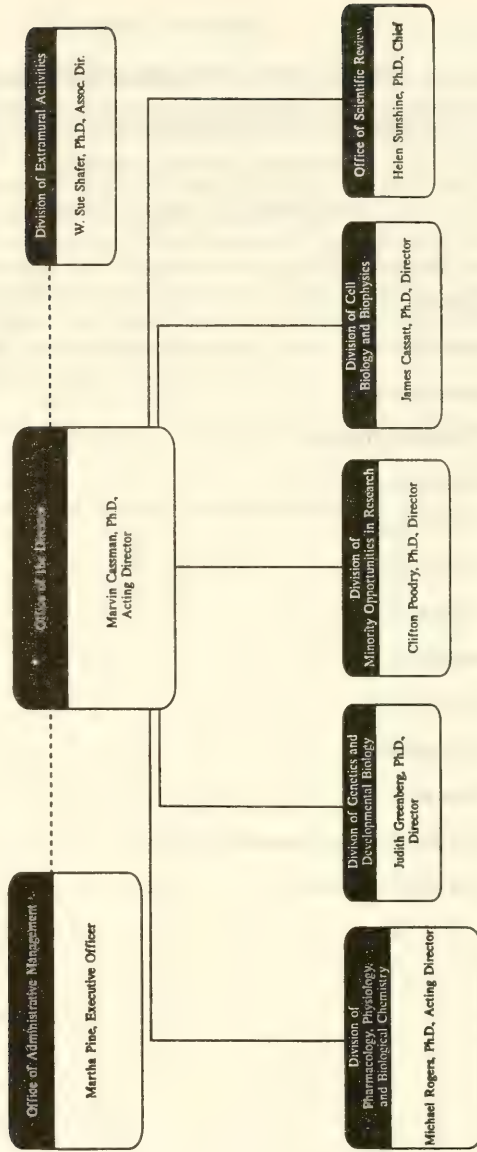
JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

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NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

National Institute Of General Medical Sciences

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

For carrying out section 301 and title IV of the Public Health Service Act with respect to general medical sciences, \$936,573,000.

Note— A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$877,113,000	\$946,971,000	\$936,573,000
Reduction in accordance with P.L. 103-333.....	-227,000		
Rescission in accordance with P.L. 104-19.....	-108,000		
Subtotal, Adjusted Appropriation.....	876,778,000	946,971,000	936,573,000
Real transfer from:			
Office of Research on Minority Health, NIH, for MARC and MBRS.....	+3,375,000		
Other NIH Institutes through the NIH Director's one percent transfer authority.....	+80,000		
Comparative transfer to:			
Office of AIDS Research, NIH for HIV activities.....	—	-26,135,000	
Subtotal, adjusted budget authority.....	880,233,000	920,836,000	936,573,000
Unobligated balance, lapsing.....	-159,000		
Total, Obligations.....	880,074,000	920,836,000	936,573,000

1/ Excludes the following amounts for reimbursable activities carried out by
- this account: FY 1995—\$15,690,000; FY 1996—\$20,000,000; FY 1997—
\$20,000,000.

Also excludes funding for HIV/AIDS activities: FY 1995—\$24,664,000; FY 1997—
\$27,050,000, included in the Office of AIDS Research, NIH.

Justification

National Institute of General Medical Sciences

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
175	\$880,233,000	173	\$920,836,000	173	\$936,573,000	---	+\$15,737,000

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute of General Medical Sciences (NIGMS). Justification of NIGMS FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

NIGMS supports high-quality basic research that yields new knowledge about biological processes and the **diseases** that result when these processes malfunction. Using the tools and approaches of a **variety** of scientific fields--from biophysics to cell and molecular biology, genetics, and **chemistry**--NIGMS grantees are working as detectives on the biggest case of all: unraveling the **mysteries** of life.

Within the past year alone, scientists supported by NIGMS have made major advances in understanding how a single cell divides into two cells with different fates, how cells repair damage to their DNA, how proteins fold, and how genes control circadian rhythms. These and other research achievements are described in more detail below, and they serve as examples of the many scientific breakthroughs made possible with NIGMS support. Findings made by NIGMS grantees often have broad applications in many fields--from cancer and genetic disorders to immunology and **aging**. They lead to improvements in disease treatment, diagnosis, and prevention, and they **also have** a multitude of uses in the commercial sector--most notably in the biotechnology, **pharmaceutical**, and agricultural industries. Many times, however, the specific applications **could not** have been predicted when **the** research was undertaken.

The economic impact of NIGMS support is underscored by two recent studies of patents awarded in the years 1987-88 and 1993-94. The studies, performed by CHI Research, Inc. (a private consulting group with expertise in patent citation analysis), found that NIGMS was the third most frequently cited government funding source for the research underlying patents issued in those years. Moreover, for both periods, NIGMS was the fifth most frequently cited of **any** funding source, public or private. These results are a clear indication that NIGMS research is being commercialized, and is benefiting the **economy** as well as improving health.

Another area in which NIGMS makes important contributions is research training. The Institute's multidisciplinary programs provide high-quality training environments to outstanding students who help meet the needs of industry and academia. This, in turn, aids the Nation in maintaining its international leadership in science.

Story of Discovery: The Case of the Shrinking Chromosome Tips

It was quintessential basic research that led three NIGMS grantees to make discoveries that now have implications for the understanding of cancer and aging. The year was 1978, and a team of scientists at Yale University was studying the chromosomes of a somewhat unusual model organism, a single-celled creature called Tetrahymena thermophila. The researchers, Dr. Joseph Gall and his postdoctoral fellow, Dr. Elizabeth Blackburn, knew that structures at the tips of the chromosomes, called telomeres, played an important protective role by preventing the ends of the chromosomes from degrading or fusing with one another, and they wanted to learn more about the composition of these structures. They hoped this approach would help them solve a longstanding puzzle: why chromosomes do not lose genetic information with each round of cell division. This loss would be expected because the enzyme that copies chromosomes before cells divide must attach to the ends of the chromosomes in order to function. As a result, a bit of each chromosome is not copied. Theoretically, after many rounds of cell division—enough to generate a mature organism from a fertilized egg—there should be no DNA left. Clearly, cells have developed a way around this problem, but the mechanism remained a mystery.

Drs. Gall and Blackburn chose Tetrahymena for their studies because the organism has a large number of tiny chromosomes, and therefore about 200 times as many telomeres as in a human cell. They found that telomeres are nothing more than a short sequence of DNA building blocks, repeated many times.

At that time, Dr. Blackburn left Yale to set up her own laboratory at the University of California, Berkeley (she has since moved to the University of California, San Francisco). She and other scientists examined telomeres in different species and found them to be structurally similar, although there were variations in the composition of the DNA sequence and the number of repeats. In 1985, Dr. Blackburn and her graduate student, Carol Greider (who is now an independent investigator at Cold Spring Harbor Laboratory in New York) were the first to describe telomerase, the enzyme that keeps telomeres from getting smaller.

As a result of the groundbreaking work of these three scientists, we now know that telomeres enable chromosomes to maintain their integrity, and we understand a great deal about how the process works. The enzyme that copies chromosomes before cells divide attaches to the telomeres, which grow shorter with each cell division. In Tetrahymena, telomerase then adds telomeric sequences back to the chromosome ends, so that the chromosomes' proper length is maintained. In most normal human cells, however, telomerase activity ceases shortly after birth, so the telomeres do become progressively shorter. Eventually, after 50 to 100 cell divisions, the telomeres are nearly gone and, some scientists think, rather than risking the loss of crucial genetic information, the cells die. In this way, telomeres may serve as a sort of "molecular clock" that tells a cell how old it is and when to stop dividing.

Cancer cells, however, divide uncontrollably, and researchers have wondered whether telomeres would offer any clues to this aberration. Findings made since 1989 by Dr. Greider and a number of other investigators indicate that in cancer cells, telomerase is somehow reactivated or the cells develop some other mechanism to keep their telomeres from shortening with each cell division. As a result, the signal to stop dividing is lost. The findings imply that inactivating telomerase or other means by which cancer cells maintain telomere length might lead to a new type of anticancer therapy.

These discoveries, combined with the isolation of human telomeres in 1988 and ongoing work to learn more about the structure and function of telomerase, have led to an explosion of research on human telomeres. In addition to the studies of telomeres and cancer,

scientists are pursuing the correlation between telomere length and the aging of both individual cells and entire organisms. Some speculate that this work could eventually lead to treatments for cells that wear out relatively early, such as those in the coronary arteries or the immune system.

The relatively rapid progress of telomere research from basic studies to potential disease applications underscores the value of learning more about biological processes. It is not always possible to predict at the outset where such basic research might lead, but history has shown that unlocking the secrets of life invariably opens new avenues for improving it.

Research Advances

NIGMS supports research in three broad areas: cell biology and biophysics; genetics and developmental biology; and pharmacology, physiology, and biological chemistry. Key advances in each of these areas are described in the sections that follow.

CELL BIOLOGY AND BIOPHYSICS

Research on cell biology and biophysics is aimed at understanding cellular components and how they interact to maintain the function of the cell and the organism. Scientists want to learn more about cell organization, movement, and division; cell membranes; and the detailed structures of biologically important molecules like DNA, RNA, and proteins. Determining the structures of such molecules is a key step in understanding their roles in certain diseases.

A Step Closer to Understanding How Proteins Fold: Scientists are now one step closer to solving a problem that they have struggled with for 40 years--determining how proteins fold into the three-dimensional shapes crucial for their function. Proteins control nearly every system in our bodies. Antibodies, enzymes, and many hormones are proteins. Diseases like cystic fibrosis, sickle cell anemia, and some cancers result from defects in proteins. As a result, there is great interest in identifying the genes that code for these defective proteins. Genes tell only half the story, though. They dictate the sequence of amino acids that make up a protein, but the actual function of a protein comes from its folded structure.

It is much easier to determine a protein's amino acid sequence than it is to decipher its three-dimensional structure. Although the sequence contains all the information necessary for correct folding, scientists still cannot predict a protein's final shape from its sequence.

Now, Dr. George Rose and postdoctoral fellow Dr. Rajgopal Srinivasan at The Johns Hopkins University have developed a method that promises to come closer than ever before to cracking the protein folding code. The method, embodied in a computer program called LINUS, uses sequence information to predict surprisingly accurate three-dimensional protein structures. By making it easier and faster to determine the structures of proteins from their sequences, this work could improve understanding of a variety of biological processes and diseases. It could also speed the development of drugs that act on target proteins, and it could be used in conjunction with the Human Genome Project to classify proteins that might be involved in genetic disorders.

Delineating Protein Processing Pathways: A newly synthesized protein is not functional until it has moved through a series of cellular compartments that fold, package, sort, and label it for delivery to its ultimate destination within or outside the cell. A number of disorders--including cystic fibrosis--are thought to arise when elements of this processing system go awry, so understanding the system's normal functions is an area of tremendous interest to

basic researchers supported by NIGMS. One of these scientists is Dr. Ari Helenius of the Yale University School of Medicine, who is a leader in the study of protein processing in the first component of the system, the endoplasmic reticulum (ER).

Dr. Helenius has made significant contributions to delineating the steps in protein processing in the ER, the roles of various "helper" proteins, and the quality control mechanisms used in the ER to distinguish correctly folded and assembled proteins from incompletely folded, misfolded, or incompletely assembled products. Only correctly folded and assembled proteins are exported to the next component of the processing system.

Recently, Dr. Helenius described the key roles played by a pair of proteins in increasing the efficiency of processing in the ER. These proteins, calnexin and calreticulin, are called "chaperone" proteins because they attach to newly formed proteins and promote correct folding by preventing undesired interactions between different parts of a single protein or between different proteins.

In addition to cystic fibrosis, other diseases that may involve defects in protein processing in the ER include alpha-1-antitrypsin deficiency (which can lead to cirrhosis of the liver and emphysema), retinitis pigmentosa (a degenerative eye disease), glioblastoma (a form of brain cancer), and scurvy. Dr. Helenius' research also has relevance for biotechnology, which faces a continuing problem in producing large quantities of desired proteins in host cells. Often, the proteins are not folded properly in the ER, which renders them unusable and limits their large-scale production.

Getting Therapeutic Molecules into Cells: Most protein-based pharmaceuticals work by binding to specialized receptors on cell surfaces. Until recently, scientists have lacked a feasible way to deliver drugs into cells, which is required for antiviral and other therapies. A recent breakthrough in this area was spearheaded by Dr. Yao-Zhong Lin and his coworkers at the Vanderbilt University School of Medicine.

Currently, scientists must use harsh chemical treatments or tedious microinjections to force potentially therapeutic molecules into cells. Using knowledge of the inner workings of cells gleaned through years of basic research, Dr. Lin's team has discovered a way to get the job done by using the cell's own machinery—but in reverse.

Dr. Lin's group took advantage of a special amino acid sequence that cells use to dispatch proteins outside the cell. The scientists discovered that this dispatch process also works in reverse. By tacking this sequence onto functional bits of synthetic proteins, Dr. Lin's group managed to trick cells in test tubes into absorbing the protein pieces.

Getting large molecules into cells is only half the battle, however. Once inside, the molecules must function properly. Dr. Lin's group has also tackled this problem. They concentrated their efforts on a molecule called NF- κ B, which is involved in inflammation and in activating viral genes, including those of the human immunodeficiency virus (HIV). Using the new technology, the scientists tricked cells into absorbing a synthetic segment of NF- κ B. This NF- κ B interfered with the cell's natural NF- κ B, indicating that the synthetic segment was working correctly and raising the possibility that this approach might someday be developed for antiviral or anti-inflammatory uses.

A Better Picture of Why Asbestos is Carcinogenic: Evidence that asbestos is a potent carcinogen caused schools, businesses, and homeowners to rip out ceiling tiles and insulation and replace them with asbestos-free materials. Although scientists have known for decades that asbestos causes a wide variety of diseases, including lung cancer, they never knew exactly how it does so. This year, for the first time, the mechanism by which asbestos causes

DNA damage--which can result in cancer--has been observed and videotaped in living cells by Dr. Conly L. Rieder and coworkers at The Wadsworth Center in Albany, New York. The scientists used new lung cells for their studies because the cells are large, easy to see into, and their biochemistry closely resembles that of human lung cells.

The scientists' videotapes reveal that some long, thin asbestos fibers needle their way into the region of a cell where chromosomes are being separated prior to cell division. Sometimes, the spearlike asbestos fibers snag, sever, or stab chromosomes, damaging DNA and potentially disrupting chromosome sorting. Fortunately, in most cases cell division proceeds normally despite the presence of asbestos fibers. But once asbestos fibers are lodged inside cells, they continue to be passed on to each generation of cells, increasing the likelihood that at some point the fibers will produce carcinogenic damage. The insights provided by Dr. Rieder's team are an important step toward preventing or treating that damage.

GENETICS AND DEVELOPMENTAL BIOLOGY

Studies in this area seek a better understanding of fundamental genetic processes, such as the intricate machinery that translates genetic instructions contained in the DNA into the myriad of proteins that catalyze and carry out all life processes. Understanding this machinery on the most fundamental level provides scientists with many ways in which to intervene to diagnose, prevent, or treat diseases.

Discovery of an Early Step in Cell Differentiation: Dr. Richard Losick of Harvard University and his collaborators have found answers to one of the most fundamental questions in developmental biology--what triggers a dividing cell to give rise to progeny with different fates. This work is a major advance in understanding the central biological mechanism of cell differentiation.

Dr. Losick has been working on complex biochemical pathways in the single-celled organism *Bacillus subtilis* for many years. He is particularly interested in the molecular mechanisms involved in a process called asymmetric division, which leads the organism to produce two progeny cells of different sizes. This results in differences in the concentration of a specific enzyme in the two daughter cells. The research results indicate that this concentration difference alone is sufficient to initiate different developmental pathways in the two offspring, leading to cells of two dramatically different types. The discovery that a quantitative difference in the concentration of an enzyme can yield a qualitative change in developmental fate is both striking and significant.

Because key molecular processes tend to be similar in the cells of both higher and lower organisms, this work should help scientists understand how differentiation occurs in many species, including humans. This, in turn, is expected to shed light on the mechanisms involved in a wide range of disorders, especially those that occur in the early stages of development.

Gene Family Will Help Scientists Study DNA Repair and Cancer: Scientists recently found a gene that, when defective, causes ataxia telangiectasia (AT), a hereditary disease characterized by a wide spectrum of neurological and circulatory defects, extreme sensitivity to X-rays, and a greatly increased risk of cancer. Even unaffected carriers of this gene have an increased cancer risk, and perhaps 9 percent of breast cancers in the United States may be related to a mutation in the gene, which the scientists named *atm*. Thanks to many years of basic biochemical studies using lower organisms, researchers are now discovering interesting similarities between the *atm* gene and a large family of genes found in these models. The work is also shedding light on possible mechanisms of action for the *atm* gene.

Dr. Leland Hartwell of the University of Washington and his colleagues have shown that a yeast gene that is similar to the human *atm* gene is a so-called "checkpoint gene." Its role is to delay the division of a radiation-damaged cell until the damaged DNA has been repaired. Dr. Thomas Petes of the University of North Carolina and his colleagues have found another yeast gene that is similar to the *atm* gene but that maintains the length of telomere sequences at the ends of chromosomes. The discovery of the similarities and differences between these genes should greatly aid understanding of the genetic basis for the cellular defects associated with mutations in the human *atm* gene.

Control of Gene Expression: Researchers have long been interested in the cellular mechanisms that cause genes, whole groups of genes, and even whole chromosomes to be inactive, or "silent." This process is very important for normal development in higher organisms. The molecular mechanisms of large-scale gene repression are very complex, and progress in understanding these processes has been slow. Now, researchers are gaining insight into the structural elements that are responsible for the silent areas on chromosomes.

Dr. David Shore of Columbia University and his colleagues have shown that the binding of certain silencing factors to specific DNA sites in yeast is the initial step in the formation of a silenced domain. Working with more complex organisms--in this case, fruit flies--Dr. Welcome Bender of Harvard Medical School and his colleagues have found multiprotein complexes, which are stabilized by the cooperative binding of still other proteins, that silence groups of genes during development. Because there are similar proteins in mammals, this model may also help explain gene silencing in higher organisms.

New Studies Shed Light on Clock Genes: Molecular circadian "clocks" that recognize the presence or absence of visible light perform key regulatory functions for a wide variety of species, from plants to humans. Because circadian rhythms are important to regulating human sleep-wake cycles, understanding the basic molecular mechanisms that control these rhythms may help humans treat or prevent jet lag and sleep disorders, as well as certain types of depression. Understanding circadian rhythms in plants and animals should have broad applications for the biotechnology and agricultural industries. For example, manipulating circadian rhythms might allow farmers to adjust when plants flower and go to seed, or enable them to produce drought-resistant plants by controlling the opening and closing of leaf pores.

Recent work by several NIGMS grantees is helping biologists understand the cellular interactions that regulate molecular clocks. Dr. Jay Dunlap of Dartmouth Medical School and his colleagues have found that the initial event in resetting the circadian clock in a bread mold is the activation of a gene called *freq*. This is the first molecular explanation for how circadian clocks are synchronized with the 24-hour cycle of light and darkness. Dr. Michael Rosbash of Brandeis University and his colleagues have discovered that interactions between fruit fly proteins that are coded for by the *per* gene are at the heart of the circadian clock's ability to compensate for temperature fluctuations. This discovery is important because it represents the first molecular explanation for the ability of circadian rhythms to remain stable despite a wide range of temperature changes. Dr. Nam-Hai Chua of Rockefeller University and his colleagues have engineered plants to glow when the genes controlling their circadian rhythms became active, enabling the researchers to identify plants with mutant circadian rhythms. This work provides a method for rapidly and easily identifying circadian rhythm mutants in plants, and it should prove very important for dissecting the molecular components of plant circadian clocks.

PHARMACOLOGY, PHYSIOLOGY, AND BIOLOGICAL CHEMISTRY

The research that NIGMS supports in this area ranges from fundamental studies in chemistry to the elucidation of biochemical and cellular mechanisms that may serve as new targets for drug design. Grantees are investigating chemical and biotechnological methods for synthesizing new drugs, the biochemical pathways involved in cellular functioning, the genetic and metabolic factors affecting drug action in humans, the body's response to trauma and burn injury, and the molecular mechanisms of action of local and general anesthetics. The results of these studies improve our understanding of how the body works and pave the way for the discovery and development of new drugs.

DNA Repair Studies Provide Clues to Human Diseases: For any organism to live, grow, and reproduce, its cells must continually divide. Whenever a cell divides, its DNA must be accurately replicated and distributed between two daughter cells. Any errors in the DNA that are passed on could cause devastating consequences, including cancer and various genetic diseases. In an effort to predict, prevent, or reduce such havoc, many scientists are striving to learn more about how cells repair damage to their DNA.

Ultraviolet radiation from the sun is one of the most common causes of DNA damage, and it is largely responsible for the thousands of skin cancer deaths in the United States each year. Some of those deaths might be prevented if humans possessed a single enzyme found in many other organisms. The enzyme, called photolyase, repairs damage to DNA caused by the sun's ultraviolet rays. Details of the enzyme's inner workings and three-dimensional structure were revealed this year by a group of scientists that included Dr. Aziz Sancar of the University of North Carolina School of Medicine, Chapel Hill, and Nobel laureate Dr. Johann Deisenhofer of the University of Texas Southwestern Medical Center at Dallas (who is not an NIGMS grantee). This improved knowledge of the enzyme might one day make it possible to develop photolyase gene therapy for people who suffer from a rare disease called xeroderma pigmentosum. Those with the disease have defective DNA repair systems, develop multiple skin cancers in childhood, and rarely live beyond their 20's.

Developing Longer-Acting Local Anesthetics: Over the past two decades, researchers have tried to develop local anesthetics whose action lasts for days or weeks. Such treatments would be invaluable to people who are in chronic pain, including those in the final stages of a terminal illness. Until recently, the search has been unsuccessful.

Now, using information from years of research on how anesthetics work in the body, Dr. Ging Wang and his coworkers at the Brigham and Women's Hospital in Boston have developed a potential new local anesthetic that appears to work much longer than lidocaine, the most commonly used local anesthetic. The anesthetic effects of lidocaine, which is employed in a host of procedures—including eye surgery, hernia repair, and obstetrical surgery—last only about an hour. In tests on rats, the new compound, named tonicaine, worked nine times longer and produced no adverse side effects. And, unlike lidocaine, tonicaine appears to allow muscle movement while it dulls pain.

Slime Mold Studies May Lead to Therapy for a Rare Disease: All cellular proteins are synthesized near the cell's nucleus, but from there, they are scattered to every corner of the cell. One way the cell directs proteins to their final destination is by using special carbohydrate chains that act as molecular routing slips. Defects in the attachment of these carbohydrates—a process called glycosylation—can cause a number of severe disorders. One of these, a rare and serious disease called carbohydrate-deficient glycoprotein syndrome (CDGS), may soon be treatable, thanks to the efforts of Dr. Hudson Freeze and his colleagues

at the La Jolla Cancer Research Foundation in La Jolla, California. The scientists' work provides insight into the overall process of glycosylation, and their findings may be applicable to other disorders with a similar biological basis.

Dr. Freeze's knowledge of carbohydrate metabolism came from his years of research on a model organism, the common slime mold. He applied this knowledge to determine what may go wrong with glycosylation in CDGS, since cells from people with the disease have glycosylation defects similar to those Dr. Freeze had observed in slime molds. Using laboratory cultures of cells from people with CDGS, he discovered a possible cure for the problem—an inexpensive treatment with a sugar called mannose. Dr. Freeze is now collaborating with scientists in Scandinavia to begin clinical studies of mannose therapy for CDGS.

A Bacterial Enzyme that Degrades Neurotoxins: On March 20, 1995, an attack on the Tokyo subway system with Sarin nerve gas left at least 10 people dead and thousands injured. Sarin is a potent neurotoxin from a family of chemicals called organophosphates. Similar compounds are commonly used in insecticides, which work by inactivating acetylcholinesterase, an enzyme that is necessary to transmit nerve impulses. In addition to poisoning insects, these compounds also pose significant hazards to human health and to the environment.

NIGMS-funded researchers have recently characterized a bacterial enzyme that efficiently degrades organophosphates, making it an excellent candidate for bioremediation efforts. The three-dimensional structure of the enzyme, called phosphotriesterase (PTE), and the mechanism by which it inactivates organophosphates, were determined by a group of scientists that included Dr. Frank Raushel at Texas A & M University. This information is essential for engineering variants of the enzyme for commercial use. One such commercial application is already under way at Rhizogenics Corporation in Bainbridge Island, Washington, where Dr. Clement Furlong and his coworkers are developing a process for the large-scale production of an enzyme related to PTE. Rhizogenics estimates that the potential annual market for such bioremediation products could exceed \$50 million.

Special Programs

MINORITY OPPORTUNITIES IN RESEARCH

NIGMS has a longstanding commitment to increasing the number and capabilities of underrepresented minority individuals engaged in biomedical research. The focal point within the Institute for this effort is the Division of Minority Opportunities in Research (MORE). The division's goal is to encourage more minority students to pursue training for scientific careers and to enhance the science curricula and research capabilities of faculty at institutions with substantial minority enrollments.

The division has three components: the Minority Access to Research Careers (MARC) Branch, the Minority Biomedical Research Support (MBRS) Branch, and a section that handles special initiatives. MORE's activities give NIGMS the lead role at NIH in research and research training activities targeted to underrepresented minorities.

Minority Biomedical Research Support Branch: MBRS is the largest minority program at NIH. MBRS awards grants to minority institutions to support research projects by faculty members and to provide opportunities for students to work as part of a research team. This support has the added benefit of strengthening the institutions' biomedical research capabilities. Awards are also made to permit enrichment activities, such as attendance by faculty and students at scientific meetings and participation in research during the summer at

off-campus laboratories. In FY 1995, 592 faculty members at 100 institutions worked on 534 MBRS research projects, and 760 undergraduate and 356 graduate students participated in these projects as research assistants.

Several initiatives are being planned for FY 1996. One responds to the continuing need for large pieces of equipment to be shared by many users. Another encourages mini-conferences to stimulate collaborative research among minority institution faculty. A third would provide funding for well-planned evaluation activities.

Minority Access to Research Careers Branch: The MARC Branch provides special research training opportunities for students and faculty at institutions with substantial minority enrollments. MARC enables grantee institutions to develop and strengthen their biomedical research training capabilities. As a result, these schools are able to graduate more students who go on to doctoral study and pursue biomedical research careers.

MARC accomplishes these goals through Undergraduate Student Training in Academic Research (U*STAR) institutional grants, predoctoral fellowships, faculty predoctoral and senior fellowships, a visiting scientist program, and grants for MARC ancillary activities. In FY 1995, 582 students at 60 institutions participated in the honors undergraduate program, 6 faculty members received training and/or degrees through the faculty fellowship program, and 75 students received MARC predoctoral fellowships.

The U*STAR grant mechanism, which replaces the MARC Honors Undergraduate Research Training (HURT) award, is new for FY 1997. Its objective--increasing the number of minority scientists pursuing research careers--is the same as that of its predecessor. The most significant changes are that each applicant institution is encouraged to design a program that emphasizes its environment, mission, and strengths, as well as to set specific objectives and measurable goals against which the program will be evaluated when it recompetes for continued funding. Also, U*STAR will not provide stipends for freshman and sophomore students, but it could support pre-MARC student development activities. Although NIGMS will no longer accept applications for HURT awards, the policies and provisions for current recipients of HURT grants will not change until the end of their present grant period.

An extensive evaluation of the HURT program was completed in August 1995. This evaluation found that MARC has been quite successful in its contribution to the progress of individuals toward Ph.D. degrees in the biomedical sciences. MARC graduates are over 2.5 times more likely to enter graduate school than other minority bachelor's degree recipients in biology and chemistry. However, the broader statistics show that the percentage of underrepresented minorities with Ph.D.'s in the biosciences has changed relatively little over the past 16 years, indicating that there is still a need for progress in this area.

Special Initiatives: MORE supports several special initiatives that strive to develop new approaches for the recruitment and retention of minority biomedical scientists. Individuals supported through these special initiatives range from high school students to faculty members. One such initiative is called Bridges to the Future. This program, which is administered by NIGMS in cooperation with the NIH Office of Research on Minority Health, encourages students in associate's or master's degree programs to make the transition to the next level of training (the bachelor's or Ph.D. degree) toward careers in biomedical research. Since the inception of the Bridges initiative in 1992, NIGMS has supported 61 programs, 6 of which received initial funding in FY 1995.

Recently, NIGMS introduced an interactive program on the World Wide Web for tracking students and reporting progress made on Bridges awards. Information obtained through this program, which is named E-STAR (for Electronic Student Tracking and Reporting), will help shape the future of the Bridges initiative. If E-STAR is successful, it can serve as a model for similar systems to be used in administering other NIGMS programs.

The division also supports the MORE Faculty Development award. This enables eligible faculty members to update or enhance their research skills by spending a summer (or one academic term) every year for 2 to 5 years in full-time research in a research-intensive laboratory outside their home institutions. Awardees may also enroll in one academic course per term in fields directly related to their research.

A new Initiative for Minority Student Development promotes innovative programs to help develop the research skills and academic competitiveness of underrepresented minority students at the undergraduate, graduate, and post-clinical doctoral levels, whether they are at a minority or majority institution. Support for student participation in research projects is only one of the allowable costs. Institutions are encouraged to develop new strategies to motivate and then develop the potential of underrepresented students. A feature of the initiative is that it is up to each institution to devise its own plan, goals, and measurable objectives to address the problem.

Finally, MORE supports a program of national predoctoral fellowships for minorities. This program, which NIGMS established 5 years ago, became an NIH-wide initiative in FY 1995. The division awarded 24 fellowships in FY 1995, bringing the total number of fellows since the program's inception at NIGMS to 187.

PHARMACOLOGY RESEARCH ASSOCIATE PROGRAM

NIGMS has a small, but unique, intramural research program, known as the Pharmacology Research Associate (PRAT) Program. Under its auspices, a group of recently trained scientists is selected each year for a 2-year period of postdoctoral research experience under the direction of preceptors in NIH intramural laboratories. The goal of this program is to develop topflight leaders in pharmacological research who will take key positions in academic, industrial, and government research laboratories. PRAT fellows work in such cutting-edge research areas as neurobiology, neurochemistry, the mechanisms of action and effects of abused drugs, endocrinology, tumor biology, and signal transduction.

Since its establishment 30 years ago, 302 scientists have graduated from the PRAT Program. It is known that at least 265 (88 percent) of them have entered research careers. Among these, 124 (47 percent) are located at academic or independent research institutions, 99 (37 percent) are at NIH or other Federal research facilities, and 42 (16 percent) are at pharmaceutical firms. Thirty-three percent of the PRAT graduates who are engaged in research possess an M.D. degree, indicating that the program has succeeded in attracting a large number of physicians and directing them into research careers instead of into clinical practice.

RESEARCH MANAGEMENT AND SUPPORT

The Research Management and Support budget provides funds for salaries, equipment, supplies, and other administrative expenditures that support the NIGMS extramural and administrative staff. A major portion of these funds is reserved for the scientific review and administration of grants and contracts, and for related fiscal stewardship functions. Additionally, the funds allow the Office of the Director to direct and oversee the Institute's scientific program activities. Through working relationships with the scientific, academic, and

grantee communities, NIGMS remains conscious of the public's health and research concerns; these are reflected in the development and planning of the Institute's programs and policies. NIGMS also continues to evaluate its existing research portfolio to determine the need for new or expanded areas of investigation based on promising areas of biomedical research.

The Research Management and Support budget also funds services provided by central NIH components, such as the Division of Research Grants, that are not eligible to receive direct Congressional appropriations; program evaluation studies; and the National Advisory General Medical Sciences Council.

In FY 1997, NIGMS will continue to streamline management strategies and administrative processes to enhance its effectiveness and efficiency in support of its mission. The Institute has already taken significant steps toward automating several grants processing procedures, including building an NIGMS grants database and developing document imaging and electronic workflow systems.

BUDGET POLICY

In the FY 1997 President's Budget Request, the NIGMS support for research project grants (RPGs) would increase by 1.7 percent over FY 1996. NIH plans to revise average cost increases identified in the Cost Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 3,376 total RPGs, an increase of 31 total RPGs over FY 1996.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Research grants:						
Research projects						
Noncompeting.....	2,146	\$456,143,000	2,413	\$531,194,000	2,524	\$583,662,000
Admin. supplemental.....	(64)	2,555,000	(120)	1,169,000	(120)	1,192,000
Competing						
Renewal.....	678	166,837,000	488	127,745,000	415	109,022,000
New.....	382	59,888,000	367	61,637,000	341	58,461,000
Supplemental.....	5	342,000	3	219,000	4	301,000
Subtotal, competing.....	1,065	227,067,000	858	189,601,000	760	167,784,000
Subtotal.....	3,211	685,765,000	3,271	721,964,000	3,284	732,638,000
SBIR/STTR	86	15,654,000	74	16,840,000	92	20,958,000
Subtotal, Research projects.....	3,297	701,419,000	3,345	738,804,000	3,376	753,596,000
Research Centers.....	9	9,192,000	9	8,389,000	9	8,389,000
Other research						
Research career program..	12	899,000	15	954,000	18	954,000
MBRS.....	100	37,105,000	103	38,181,000	103	36,181,000
Other.....	48	3,740,000	97	4,700,000	97	4,700,000
Subtotal, other research..	160	41,544,000	216	43,835,000	216	43,835,000
Total, research grants.....	3,466	752,155,000	3,570	791,028,000	3,601	805,820,000

Training:

Individual awards					
Noncompeting.....	391	9,583,000	398	10,491,000	486
Competing.....	228	5,564,000	266	6,220,000	178
Subtotal, Individual.....	619	15,147,000	664	16,711,000	664
Institutional awards					
Noncompeting.....	2,423	56,559,000	2,729	66,370,000	2,786
Competing.....	1,015	24,546,000	675	16,199,000	638
Subtotal, Institutional.....	3,438	81,105,000	3,404	82,569,000	3,404
Total, training.....	4,057	96,252,000	4,068	99,280,000	4,068
Research and development contracts.....					
	10	4,554,000	8	4,696,000	8
	FTEs		FTEs		FTEs
	14	1,019,000	14	1,010,000	14
Intramural research.....					
Research management and support.....	161	26,253,000	159	24,822,000	159
TOTAL.....	175	880,233,000	173	920,836,000	173
					936,573,000

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences
Budget Authority by Activity
(Dollars in thousands)

	1993 Actual		1994 Actual		1995 Actual		1996 Estimate		1997 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Biomedical Research.....	—	\$701,330	—	729,987	—	\$756,709	—	\$795,724	—	\$810,357	—	+\$14,633
Biomedical Research Training..	—	87,531	—	94,800	—	96,252	—	98,280	—	100,384	—	+1,104
Intramural Research.....	19	1,176	18	1,136	14	967	14	1,010	14	1,010	—	—
Research Management and Support.....	172	25,304	161	25,829	161	26,146	159	24,822	159	24,822	—	—
Total Obligations....	191	815,341	179	851,552	175	880,074	173	920,836	173	936,573	—	+15,737
Unobligated balance lapsing.....	44			16		159		—		—		—
Total, Budget Authority.....	191	815,385	179	851,568	175	880,233	173	920,836	173	936,573	—	+15,737

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences
Summary of Changes

1996 Estimated budget authority.....	\$920,836,000
1997 Estimated budget authority.....	<u>936,573,000</u>
Net change.....	+15,737,000

Changes:	1996 Estimate Base		Change from Base	
	<u>FTE</u>	<u>Budget Authority</u>	<u>FTE</u>	<u>Budget Authority</u>
<u>A. Built-in:</u>				
1. Intramural				
a. Within grade increases.....		\$719,000		+\$12,000
b. Annualization of pay raise.....		719,000		+5,000
c. FY 1997 pay increase.....		719,000		+17,000
d. Centrally furnished services.....		262,000		-3,000
e. Inflationary increase.....		29,000		<u>+1,000</u>
Subtotal.....				+32,000
2. Research Management & Support				
a. Within grade increases.....		9,531,000		+168,000
b. Annualization of pay raise.....		9,531,000		+61,000
c. FY 1997 pay increase.....		9,531,000		+220,000
d. Centrally furnished services.....		7,620,000		-137,000
e. FECF unemployment compensation.....		9,531,000		+2,000
f. Service and supply fund increase.....		5,136,000		+113,000
g. Inflationary increase.....		2,535,000		<u>+55,000</u>
Subtotal.....				+482,000
<u>B. Program:</u>				
	<u>No.</u>		<u>No.</u>	
1. Research projects grants:				
a. Noncompeting.....	2,413	532,363,000	+111	+32,491,000
b. Competing.....	858	189,601,000	-98	-21,817,000
c. SBIR/STTR.....	<u>74</u>	<u>16,840,000</u>	<u>+18</u>	<u>+4,118,000</u>
Subtotal.....	3,345	738,804,000	+31	+14,792,000

2. Training.....	99,280,000	+1,104,000
3. Research and development contracts.....	4,696,000	-159,000
4. Intramural.....	1,010,000	-32,000
5. Research Management & Support..	24,822,000	<u>-482,000</u>
Total changes.....		+15,737,000

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	173	173	—
Full-time equivalent of overtime and holiday hours.....	1	1	—
Average SES salary.....	\$109,419	\$112,592	+\$3,173
Average GS grade.....	10.2	10.2	—
Average GS salary.....	\$34,887	\$35,878	+\$991
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).....	54,726	56,315	+1,587
Average salary of ungraded positions.....	37,094	38,169	+1,075
Personnel compensation:			
Full-time permanent.....	\$7,453,000	\$7,791,000	+\$338,000
Other than full-time permanent.....	750,000	783,000	+ 33,000
Other personnel compensation.....	213,000	223,000	+10,000
Special personal services payments.....	—	—	—
Subtotal, personnel compensation.....	8,416,000	8,797,000	+381,000
Personnel benefits.....	1,824,000	1,906,000	+82,000
Benefits for former personnel.....	10,000	10,000	—
Travel and transportation of persons.....	233,000	233,000	—
Transportation of things.....	53,000	53,000	—

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Object - continued

	1996 Estimate	1997 Estimate	Increase or Decrease
Rental payments to others.....	7,000	7,000	—
Communications, utilities, and miscellaneous charges.....	256,000	256,000	—
Printing and reproduction.....	340,000	340,000	—
Other services:			
Consulting services.....	97,000	97,000	—
Other services.....	175,000	175,000	—
Purchases from govt. accts.....	15,787,000	15,324,000	-463,000
Operation and maintenance of facilities....	81,000	81,000	—
R&D contracts.....	2,243,000	2,084,000	-159,000
Operation and maintenance of equipment	271,000	271,000	—
Supplies and materials.....	127,000	127,000	—
Equipment.....	544,000	544,000	—
Grants, subsidies, and contributions.....	890,308,000	906,204,000	+15,896,000
Insurance Claim & Indemnities.....	64,000	64,000	—
Total Budget Authority by Object.....	920,836,000	936,573,000	+15,737,000

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Administrative Costs

	1996 Estimate	1997 Estimate	Increase or Decrease
Personnel compensation:			
Full-time permanent (11.1).....	\$7,453,000	\$7,791,000	+\$338,000
Other than full-time permanent (11.3).....	750,000	783,000	+33,000
Other personnel compensation (11.5).....	213,000	223,000	+10,000
Special personnel services payments (11.8).....	—	—	—
Total, personnel compensation (11.9).....	8,416,000	8,797,000	+381,000
Civilian personnel benefits (12.1).....	1,824,000	1,906,000	+82,000
Benefits for former personnel (13.0).....	10,000	10,000	—
Travel (21.0).....	233,000	233,000	—
Transportation of things (22.0).....	53,000	53,000	—
Rental payments to others (23.2).....	7,000	7,000	—
Communications, utilities, and miscellaneous charges (23.3).....	256,000	256,000	—
Printing and reproduction (24.0).....	340,000	340,000	—
Other services:			
Consulting services (25.1).....	97,000	97,000	—
Other services (25.2).....	175,000	175,000	—
Purchases from govt. accts (25.3).....	10,601,000	10,138,000	-463,000
Operation and maintenance of facilities....	81,000	81,000	—
Operation and maintenance of equipment	271,000	271,000	—
Supplies and Materials (26.0).....	127,000	127,000	—
Total.....	22,491,000	22,491,000	—

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Estimate
Research and Investigation.....	Section 301	42 § 241	Indefinite	Indefinite	\$836,189,000
National Institute of General Medical Sciences.....	Title IV, Part C	42 § 285	Indefinite	Indefinite	
National Research Service Awards.....	Section 487 (D)	42 § 288	Such sums as necessary	Authorizing legislation is pending	100,384,000
Total Budget Authority...			920,836,000		936,573,000

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation ^{1/}</u>
1988	\$482,004,000	\$666,037,000 <u>2/</u>	\$650,617,000	\$632,676,000
1989	676,728,000 <u>3/</u>	623,087,000 <u>4/5/</u>	690,653,000 <u>4/</u>	690,653,000
1990	766,421,000 <u>6/</u>	692,639,000 <u>7/</u>	752,939,000 <u>8/</u>	691,278,000 <u>9/</u>
1990 Sequester	—	—	—	-9,496,000
1991	745,494,000 <u>7/</u>	693,499,000 <u>10/7/</u>	779,351,000 <u>7/</u>	760,010,000 <u>11/</u>
1991 Sequester	—	—	—	-10,000
1992	833,180,000	820,160,000	815,158,000	818,910,000 <u>12/</u>
1993	862,069,000	833,807,000	824,529,000	832,581,000 <u>13/</u>
1994	833,064,000	875,511,000	875,511,000	875,511,000
1995 <u>14/</u>	882,189,000	877,113,000	877,113,000	876,886,000 <u>15/</u>
1995	Rescission			-108,000
1996	907,674,000 <u>14/</u>	946,971,000	897,465,000 <u>14/</u>	946,971,000
1997 <u>14/</u>	936,573,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ Does not include funding for AIDS research (\$11,100,000). Proposed for consolidation at the Office of the Assistant Secretary for Health.

4/ Includes \$11,100,000 for AIDS research.

5/ Excludes \$69,841,000 in NRSA training programs not considered.

- 6/ Excludes funds for AIDS research proposed for consolidation in the Office of the Assistant Secretary for Health. Includes funds for the Human Genome Research Initiative.
- 7/ Includes funds for AIDS research and the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources. Excludes funds for the Human Genome Research Initiative to be considered under a separate new appropriation account.
- 8/ Includes funds for AIDS research and funds for the Human Genome Research Initiative.
- 9/ Includes funds for AIDS research. Excludes funds for the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources, the Human Genome Research Initiative and an enacted administrative reduction of \$588,000.
- 10/ Excludes \$85,650,000 in NRSA training programs not considered.
- 11/ Excludes enacted administrative reductions of \$19,240,000 and funds transferred from other accounts for the Shannon awards.
- 12/ Excludes enacted administrative reductions of \$1,276,000 and a rescission of \$790,000.
- 13/ Excludes enacted administrative reductions of \$7,224,000.
- 14/ Excludes funds for HIV/AIDS Research Activities consolidated in the NIH Office of AIDS Research.
- 15/ Excludes enacted administrative reduction of \$227,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	35	35	35
Office of Administrative Management.....	35	34	34
Division of Extramural Activities.	49	48	48
Genetics and Developmental Biology Division.....	13	13	13
Pharmacology, Physiology, and Biological Chemistry Division....	24	24	24
Cell Biology and Biophysics Division.....	12	12	12
Minority Opportunities in Research Division.....	7	7	7
Total, NIGMS.....	175	173	173

Average GS/GM Grade

1990.....	9.8
1991.....	9.7
1992.....	10.0
1993.....	10.2
1994.....	10.0
1995.....	10.2
1996.....	10.2
1997.....	10.2

Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

EXHIBIT P

Program Administration
Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
Executive level I.....			
Executive level II.....			
Executive level III.....			
Executive level IV.....			
Executive level V.....			
Subtotal.....			
Total - Exec. Lev. Sal.....			
ES-6.....			
ES-5.....			
ES-4.....	3	4	4
ES-2.....	1	2	2
ES-1.....	1	1	1
Subtotal.....	5	7	7
Total - ES Salary.....	\$540,269	\$770,555	\$792,895
GS/GM-15.....	15	15	15
GS/GM-14.....	21	21	21
GS/GM-13.....	13	13	13
GS-12.....	27	27	27
GS-11.....	9	8	8
GS-10.....	1	1	1
GS-9.....	11	11	11
GS-8.....	6	5	5
GS-7.....	29	29	29
GS-6.....	11	11	11
GS-5.....	8	8	8
GS-4.....	7	7	7
GS-3.....	5	5	5
GS-2.....	1	1	1
GS-1.....	0	0	0
Subtotal.....	164	162	162

Grades established by Act of
July 1, 1944 (42 U.S.C. 207):

Assistant Surgeon General

Director Grade

Senior Grade

Full Grade

Senior Assistant Grade

Assistant Grade

Subtotal.....	3	4	4
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Ungraded	12	12	12
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Total permanent positions.....	184	185	185
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Total positions, end of year.....	184	185	185
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Total full-time equivalent (FTE) employment, end of year.....	175	173	173
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Average ES level.....	3	3	3
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Average ES salary.....	\$107,379	\$109,419	\$112,592
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Average GS/GM grade.....	10.2	10.2	10.2
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Average GS/GM salary.....	\$34,024	\$34,887	\$35,878
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THURSDAY, APRIL 25, 1996.

BUILDINGS AND FACILITIES

WITNESSES

DR. HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. JOHN GALLIN, M.D., DIRECTOR, CLINICAL CENTER

DR. RUTH KIRSCHSTEIN, DEPUTY DIRECTOR

ANTHONY ITTEILAG, DEPUTY DIRECTOR FOR MANAGEMENT

STEPHEN A. FICCA, ASSOCIATE DIRECTOR FOR RESEARCH SERVICES

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We continue our hearings on the National Institutes of Health, by looking at the Building and Facilities account. And we're pleased to welcome yet again Dr. Harold Varmus, the Director of NIH.

Dr. Varmus.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Thank you, Mr. Porter.

This afternoon, as you know, we're going to talk about two components of the NIH over which I have direct jurisdiction, the Office of the Director, which we'll talk about in the subsequent hour, and buildings and facilities.

Accompanying me in this portion of the discussion, to help me with some aspects of the issues I'm going to be raising are John Gallin, on my far left, who's the Director of the Clinical Center; Dr. Ruth Kirschstein, Deputy Director, who will have a great deal to say in both parts of our discussion; Steven Ficca, who is the Associate Director of the Division of Research Services; and the Deputy Director for Administration, Mr. Tony Itteilag.

OPENING STATEMENT

The role of buildings and facilities on the NIH campus, of course, is fundamental to our operation of the intramural research program, a program which has a budget of \$1.3 billion, several thousand investigators, many laboratories, and facilities not only on the Bethesda campus but also at many other sites, including Poolesville, Maryland, Frederick, Maryland, Research Triangle Park, North Carolina, the Rocky Mountain lab in Hamilton, Montana and several other sites, including Baltimore.

The management of those facilities and construction of new facilities is in the domain of the Office of Research Services, and occupies a great deal of our attention. Adequate working conditions

and safe facilities for our staff and for patients who come to our buildings are of course very high priorities for us.

Ever since the intramural program underwent its expansion, about the time of World War II, our buildings and facilities program has been a very major feature of the NIH. This year, I'm presenting the B&F budget because the budget is an unusual one. In addition to the ongoing essential maintenance and repair components of the budget, we have requested money to fund the Clinical Research Center, CRC, as I indicated to you in my opening comments last Thursday.

CLINICAL RESEARCH CENTER

Let me deal first with the construction of the CRC. I will submit most of my comments for the record, because we've gone over some of this territory before, and I want to give us time for adequate discussion of these topics.

The clinical research component of the intramural program is the pivotal component of that program. It is what makes the intramural programs at NIH unusual among research programs in the country, indeed throughout the world. It's the site of many important discoveries. It unites the campus activities in a way that really cannot be measured.

In view of the infrastructural difficulties, which have been documented now many times since the late 1980s, it is mandatory that we make dramatic changes in the site at which we carry out our clinical research. After a great deal of deliberation and consultation with a wide range of organizations, ranging from the Army Corps of Engineers to an extramural group that was assembled at the direction of your subcommittee, it has been recommended that the logical outcome of the identification of these structural deficiencies is the construction of a new building.

Our incentives to go ahead with this building were only heightened by a recent review of the management of the current Clinical Center by a committee headed by Helen Smits, the Deputy Administrator of HCFA—a study undertaken at the direction of the Secretary of HHS—that gave us a number of suggestions and directions about the way in which we manage our hospital. That report also indicated the importance of having a new building that could exploit the suggestions for enhanced efficiency that it was felt could be achieved by improved management.

In addition, our plan to build a new clinical center is part of a master plan, which has received approval in the Government planning process. The proposal that we're making, just to review it for you again briefly, is for a new hospital with 250 beds. There would be roughly 100 sites at which day care patients would be examined and treated. These are not separate rooms or even beds, but 100 stations where patients could be seen in several large rooms.

The plan also calls for additional adjacent laboratory space that in essence makes the patient-oriented activities part of a laboratory. Historically, it has been crucial to the NIH intramural program to have a close interchange between laboratory and patient-oriented activities. In the context of this new building, we hope to enhance, the strong synergy between those two components of our program.

We make this proposal in recognition of the ideas that medical care is going to become even more science based in the future, that new therapies are going to be based on the remarkable progress that's been made in molecular and cellular and genetic science, and that new means of immune therapy, gene therapy, and novel pharmacological interventions, based on understanding of enzyme mechanisms and cell biology, will require that the development of those new technologies at the clinical center be carried out with a remarkably close interaction between laboratory scientists and patient-oriented researchers.

CRC BUDGET REQUEST

We're asking that the committee appropriate \$310 million in fiscal year 1997 for the construction of this building. As you recall, Mr. Chairman, over the course of the last two years, monies have been appropriated for initial phases of the planning process, \$2.5 million in 1995, and \$23 million in fiscal year 1996. And we have used those monies in ways I could detail further to carry out the initial phases of the planning process.

DESCRIPTION OF CLINICAL CENTER

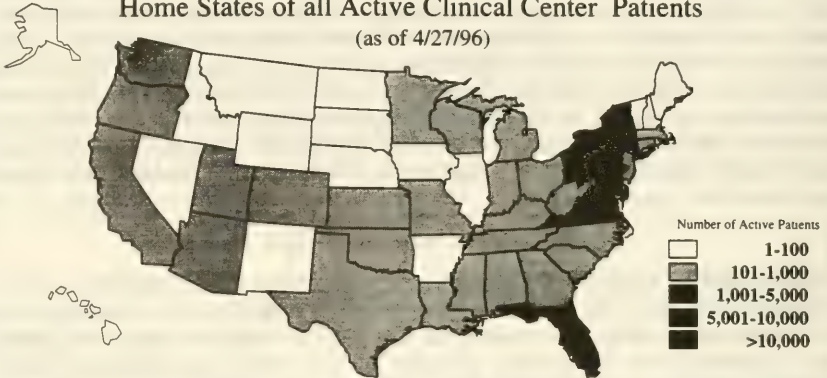
Mr. PORTER. Dr. Varmus, I'm sorry to interrupt you, but I would like you to explain particularly for the benefit of newer members who may not have been to the clinical center how the clinical center would differ and does differ, the current one, from a regular hospital, where the patients come from and why they are there, rather than at a regular hospital facility. Sort of the basics of this thing.

Dr. VARMUS. Fine. The clinical center is a national resource, indeed, an international resource. Patients are recruited from all around the country. Virtually every state in the country contributes patients. We have a map that illustrates the number of active patients as of this February, showing that virtually all states have appreciable numbers, 32,000 patients are currently enrolled in some of our thousand patient protocols. These 32,000 patients come from essentially all states, with numbers that range up to 10,000 in the immediate area around D.C., particularly in Maryland.

[The information follows:]

Home States of all Active Clinical Center Patients

(as of 4/27/96)



Alabama	147	Georgia	494	Maryland	11,771	New Jersey	918	South Carolina	302
Alaska	36	Hawaii	17	Massachusetts	275	North Carolina	626	South Dakota	20
Arizona	147	Idaho	47	Michigan	503	New Hampshire	79	Tennessee	289
Arkansas	85	Iowa	76	Minnesota	192	New York	1,383	Texas	549
California	388	Illinois	442	Mississippi	119	North Dakota	19	Utah	109
Colorado	179	Indiana	293	Missouri	206	Ohio	637	Vermont	58
Connecticut	245	Kansas	127	Montana	31	Oklahoma	149	Virginia	5,167
Delaware	201	Kentucky	159	Nebraska	56	Oregon	122	Washington	201
D.C.	2,108	Louisiana	275	Nevada	77	Pennsylvania	1,723	West Virginia	505
Florida	1,319	Maine	63	New Mexico	81	Rhode Island	57	Wisconsin	192

The clinical center was built in 1952, and initially had 517 beds. Over time, the patterns of care and experimental therapies have changed significantly, so that, at present, the number of occupied beds peaks at a little over 200 beds per day. We have appropriately downscaled as much as possible, within the configuration of the existing facility, to something on the order of 325 beds, of which about 210 or so are occupied at the peak times during the week.

[CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this number to "500 beds" for the record.]

The work that's done at the clinical center is all experimental. There are no routine patients in the clinical center. All these patients are enrolled in one or another of the roughly thousand protocols that are carried out by the approximately 15 Institutes and Centers that have active work carried out in the clinical center.

The diseases that are studied are very wide ranging. There is a large amount of work in the field of cancer; the Cancer Institute carries out about 40 percent of the clinical research in the existing clinical center. But there is also an enormous amount of work being done on less common disease, including very rare diseases.

Very recently, the Secretary of HHS and Senator Kennedy came on separate days to review some of this extraordinary work. They saw patients from all over the country who had been referred by their physicians, at a loss to either diagnose or treat these individuals. When they arrive at the Clinical Center, they find a nucleus of interest in even extraordinarily rare diseases, with world experts able to move between the laboratory and the clinic in providing accurate diagnosis and insight into the diseases. They help these individuals to develop support groups; otherwise they would be on their own, in a part of the country where these diseases are very rarely seen.

The clinical center also serves as a focus for clinical research that can respond quickly to national need. This was very dramatically portrayed at the time of the outbreak of the AIDS epidemic. AIDS patients were brought to the clinical center very early in the course of the outbreak, and they have been actively studied there ever since.

Because of the ability to **change** direction quickly, we believe that the clinical center offers **a particularly** powerful place to pursue changes in disease patterns that we know can occur as a consequence of infectious agents.

The rest of my testimony deals with the ongoing renovation and maintenance. I can submit that for the record; if you want to ask other questions about it, I would be pleased to respond.

[The prepared statement of Dr. Harold Varmus follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
Buildings and Facilities

The Buildings and Facilities appropriation provides funds for the design, construction, improvement, and major repair of clinical, laboratory, and office buildings, as well as supporting facilities, essential to the mission of the NIH. The Buildings and Facilities program has a critical and exciting impact in terms of shaping and defining the very essence of the NIH campus as we approach the twenty-first century.

The NIH has developed an updated master plan that was completed in December 1995 and approved in February 1996 for the Bethesda campus. The aging of the facilities and infrastructure, the development of new technologies, and the evolving biomedical research programs at NIH have required a new blueprint to guide future development on the campus. The new comprehensive master plan identifies programmatic requirements in terms of personnel and physical facilities; establishes concepts for future development and land use, buildings, utilities, open space, circulation and traffic management for the next twenty years; and illustrates how needs for laboratory and clinical research, administrative, and support space can be accommodated. An updated Master Plan for the NIH Animal Center in Poolesville is currently being developed and will be completed in the Fall of 1996.

The NIH is contending with an aging, deficient physical plant. The majority of the infrastructure systems are 20 to 40 years old and beyond their design life. To address these deficiencies and plan for the future, the NIH is integrating all corrective and new construction programs into a comprehensive Facilities Revitalization Program. This program represents a long-term strategy to coordinate projects and set priorities. The purpose is to support ongoing laboratory and clinical research, anticipated technological advancements and evolving research programs with safe, functional, and adaptable modern facilities for the foreseeable future.

While the NIH gives a high priority to all safety and health requirements, it has placed the highest priority on the renewal of the Clinical Center. In addition to patient related research, the Clinical Center contains approximately 40 percent of the research space on the Bethesda campus and is the keystone of the NIH Intramural Research Program. However, the utility systems within the complex are deteriorated, outmoded, obsolete, and insufficient to support modern research. The NIH has developed plans to renew the complex and address the infrastructure deterioration, consistent with the recommendations of various external reviews including the External Advisory Committee.

The Clinical Center is the heart of the NIH intramural program where many basic science discoveries are translated into clinical applications that address the Nation's health needs. The Center is the working environment for an unparalleled confluence of basic and clinical researchers with a breadth of expertise across many disciplines and diseases. The resulting combination of intellectual and physical resources fosters quick and formidable responses to new research opportunities and to emerging public health problems.

During the late 1980's, it became apparent that the Clinical Center's ability to provide ongoing patient care and research activities in a safe and reliable facility was being threatened by overcrowding and a deteriorating, inadequate utility infrastructure. In 1989, an in-house review of the facility revealed a pressing need for comprehensive building improvements. In 1991, the appropriateness of this approach was validated by an independent analysis mandated by Congress and conducted by the U.S. Army Corps of Engineers. The Corps confirmed the extent and severity of the problems in the existing Clinical Center and strongly recommended immediate and major corrective action. Subsequently, the NIH undertook a series of studies to explore the most effective solution to providing the requisite clinical research environment on the campus.

In 1994, the External Advisory Committee of the Director's Advisory Committee, NIH, concluded that the NIH's highest priority need could be met most efficiently by building a new facility immediately adjacent to, and integrated with, the existing structure. This new facility would replace the existing 500-bed patient care complex with a new state-of-the-art, 250-bed hospital connected to new laboratory space. In this approach, called the Clinical Research Center (CRC), the entire research hospital and patient care programs would be relocated to a new research hospital facility which will be served by additional new space dedicated to laboratory and program support space. This new complex will be located immediately north of the existing building complex. Following the completion and occupancy of the new addition, the existing building complex could be renovated in stages. It is estimated that the new addition will take six years to complete and will be ready for occupancy in 2002.

Funds provided in the FY 1995 appropriation of \$2.5 million were used to investigate and evaluate different project development approaches and design options for the new facility. They were also used to pay for an international design concept competition. The FY 1996 budget level includes \$23 million for architecture and engineering design and design development for the project. The FY 1997 request includes \$310 million required to carry the Clinical Center Renewal project to completion. More specifically, this request will provide for the completion of the construction documents, demolishing Building 20, preparing the site, installing the infrastructure support, and completing the construction of the new addition inclusive of associated fees for construction and project management.

NIH continues to place a high priority on the essential safety and health requirements of its facilities. In addition to the CRC, the Essential Safety and Health Improvement Initiative addresses the infrastructure upgrades to existing NIH facilities to meet critical occupational and environmental requirements to protect and support ongoing research programs, including the safety and health of NIH employees and patients. Supporting utilities need to be modernized and improved in order to meet safety and health requirements in support of the NIH research mission.

Particularly important in this initiative is the Clinical Center **Essential Maintenance and Safety (EMS)** Program which provides for the **urgently needed** restoration of the primary utility systems and the correction of **specific life safety** deficiencies. This is the minimum investment required in the existing building until the completion of the new CRC. The EMS Program will focus on safety issues, hospital accreditation, and major central system renovations to enhance reliability. Implementation of the Clinical Center EMS Program has been a crucial interim project for insuring a safe and functional facility for clinical and biomedical research for about the next 15 years, or until the Clinical Research Center Renewal Program is completed. The FY 1997 budget requests funding for the final phase to complete the EMS Program. It will provide for the restoration of smaller heating ventilating and air conditioning (HVAC) equipment distributed within lower levels of the building; required improvements of fire safety systems; and correction of emergency power deficiencies.

The Infrastructure Modernization Program (IMP), initiated in FY 1991, is in the seventh of a nine-year program to replace and expand central utility equipment and distribution systems. A critical situation has developed where sufficient and uninterrupted services to research and patient care activities cannot be ensured due to obsolete, deteriorated systems, overburdening from growth, and increasing program requirements. The IMP is critical to ensure the infrastructure capability to carry out the NIH mission and remove the possibility of a catastrophic failure of the central utility and distribution systems. This request includes funds to support expansion of the refrigeration building to house secondary pumping apparatus, chillers, additional electrical equipment and controls for the chillers and boilers in the Power Plant. Construction will also continue on a new utility distribution tunnel for underground chilled water and steam distribution piping, and to replace storm, electrical, potable water and sanitary systems.

Other funds included in the FY 1997 request for the Essential Safety and Health initiative are for the fourth year of multi-year programs to improve outdoor air quality by upgrading the power plant's infrastructure, for the phased removal of asbestos-containing materials from various NIH buildings, for the upgrade of the fire and life safety equipment of NIH buildings on the campus and at the NIH Animal Center, the elimination of barriers to persons with disabilities, the acquisition, construction and implementation of a medical pathological waste system, the revitalization of facility reliability and safety upgrades at the Rocky Mountain Laboratory in Hamilton, Montana, the study, design, and construction of a multi-year program to address indoor air quality concerns at NIH facilities and the initial funding for the design of the rehabilitation of Building 6 and the partial upgrade of Building 6A.

It is essential for the NIH to carry out major repairs and improvements to the physical plant that supports the main NIH campus in Bethesda, as well as to field stations that are the responsibility of the NIH. Projects of a recurring nature include roofs, roads, structures, and building utilities. Other projects are one-time occurrences that require immediate attention and are critical to the continuing operation of our research facilities.

The FY 1997 request for Buildings and Facilities is \$420,000,000. The request includes \$310,000,000 for the Clinical Research Center Addition and \$84,100,000 for essential safety and health improvements composed of \$11,100,000 to maintain safety of the Clinical Center; \$43,100,000 for continued funding of the site infrastructure modernization program at the NIH; \$2,900,000 to continue the power plant safety program; \$6,000,000 for the phased removal of asbestos from NIH buildings; \$2,000,000 for the continuing upgrade of fire and life safety deficiencies of NIH buildings; \$1,500,000 for the elimination of barriers to persons with disabilities; \$2,500,000 for the acquisition, construction and implementation of a medical pathological waste system; \$9,300,000 for safety and reliability upgrades at the Rocky Mountain Laboratory; \$1,500,000 for implementation of an indoor air quality improvement program; and \$4,200,000 for the modernization of Building 6/6A. The FY 1997 request also includes \$25,900,000 for the continuing program of repairs and improvements.

EXPERIMENTAL RESEARCH AT CLINICAL CENTER

Mr. PORTER. Well, let me try to distill what I think you just told us. For one thing, you've said this is a hard case hospital, is that correct? Difficult cases that—

Dr. VARMUS. Difficult cases.

Mr. PORTER [continuing]. Cannot be handled well elsewhere come to the clinical center? Is that correct?

Dr. VARMUS. That's correct.

Mr. PORTER. And it's also an experimental facility?

Dr. VARMUS. Entirely experimental.

Mr. PORTER. Where you are doing, looking at experimental treatments, perhaps?

Dr. VARMUS. Often experimental treatments that are extremely expensive and require specialized expertise available from the scientists on our campus, or require the special facilities—PET scanning, cyclotrons, other kinds of equipment and materials that would not be routinely available elsewhere.

Mr. PORTER. And why couldn't—I think I know—but why couldn't you do this experimental work in other hospitals around the country and synthesize from that, rather than having a separate facility at NIH?

Dr. VARMUS. Well, of course, some similar work is also done elsewhere around the country. We've trained a large cohort of physician scientists who have gone out to do very useful work elsewhere in the country.

But there are a number of advantages to having a centralized, large-scale hospital that's devoted entirely to research. For one thing, it's possible to accrue enough patients, even for rare diseases, to have phase one and phase two clinical studies.

These are very difficult to achieve in the General Clinical Research Centers, that normally have a very small number of beds at academic health centers. Those centers do very useful work. But they cannot achieve the number of patients to allow some of the necessary phase one and phase two trials, especially for rare diseases.

I think it's also important for the leading country in the world in biomedical research to have one center that can be used as a focal point for all patient-oriented research. It's a place that can be turned to for information and for specialized reagents; it is a resource that can direct physicians and other investigators to the right places to seek further help.

Mr. PORTER. And we're already doing this, this is simply upgrading?

Dr. VARMUS. Yes we're doing it now. But the issue at the moment, Mr. Chairman, is whether we're going to continue to do this. Dr. Gallin and I have many plans to enhance our activities and our interactions with the extramural research community. If we're going to do that and sustain the high level of work that has been carried out there, we are going to have to do something to confront the physical deficiencies in the existing building.

TRAINING AT THE CLINICAL CENTER

Mr. PORTER. And this facility, the current facility, and the one that we hope to build, also have a major teaching component, do they not?

Dr. VARMUS. They do. The current program trains many hundreds of clinical investigators. It also has recently, under Dr. Gallin's guidance, developed a formal course in clinical research. It conducts grand rounds every week that are sent by video conferencing to roughly 100 or more academic institutions around the country. I and many others in the biomedical community are products of that training program. It is a core element in instruction in clinical research.

TRANSLATION OF BASIC RESEARCH

Mr. PORTER. And it would be fair to say that this is the place where the theory meets the practice, where at the highest level, the research that has been done is attempted to be applied to real live patients in an existing hospital facility?

Dr. VARMUS. Yes, that's certainly true. Of course, that's also true of any clinical research unit. But we do it at the clinical center in Bethesda with a greater intensity and on a larger scale than can be done elsewhere.

Mr. PORTER. And this is what the clinical center has been doing since 1952?

Dr. VARMUS. That's correct.

TIMING OF CRC REQUEST

Mr. PORTER. Those are all the easy questions. Now the hard questions.

Why do we have to do this now? Why can't we wait a year or two?

Dr. VARMUS. Mr. Porter, there are some simple answers to that. The first is that the necessary groundwork has been done. That is, we have through the generosity of your committee, obtained money that allows us to carry out the initial phases of the planning process. So we are ready to initiate construction by the end of fiscal year 1997. That is, money appropriated for the construction project would begin to be obligated by the end of fiscal year 1997. So the timing is right from that point of view.

If we delayed this project, two consequences would result. First, we would have increased costs in the existing hospital, because of the need to carry out further renovations to ensure the safety of our workers and patients. Secondly, we would be entailing increased risks to those individuals. If we delay the project, we're not going to make it cost less in the end; it may indeed cost more. So at this point, the timing, in my view, is right.

ALTERNATIVES TO CRC REPLACEMENT

Mr. PORTER. Some in the extramural community have asserted that you could simply increase funding of the General Clinical Research Centers network, rather than building a new hospital, or that you could use space in the Naval Hospital or the Uniformed Health Sciences University. How do you answer those critics?

Dr. VARMUS. Well, first of all, I think essential to the excellence of the clinical center has been the remarkable synergy between the scientific program on the Bethesda campus and the patient-oriented research program. And that synergy requires very close contact.

Moreover, it requires facilities that have a special level of expertise and a special level of instrumentation. The hospital must be designed for research purposes. There's a very major difference between a hospital that has been designed for ordinary patient care and one that's designed for research.

It's been suggested by some that we look for empty beds in local hospitals in the greater Washington area. I would answer that, first of all, we would lose the synergy of having a concentrated patient-oriented research effort. But we simply don't have the facilities in those hospitals to carry out the research programs that demand sophisticated technology and adjacency of scientific expertise.

COST ESTIMATES FOR CRC

Mr. PORTER. How did you and your staff develop the cost estimates for construction of the hospital, and how is the cost per square foot compared to other recent construction projects that have a similar mission?

Dr. VARMUS. Well, Mr. Porter, when I first came to NIH, I was told that one option was to tear down the existing Building 10, which as you know is not simply the hospital, but 40 percent of our research base, and rebuild the whole unit at a cost of \$1.7 billion. That seemed extremely unlikely to me.

Fortunately, at the time that I arrived, we were also benefitted by the advice of the External Advisors Committee, headed by Drs. Paul Marks and Gail Cassell. Their suggestion was that we look carefully at current occupancy at the clinical center and try to estimate what occupancy would be like over the next 20 to 50 years, based on not simply the existing census, but other changes. For example, we're creating ways for intramural investigators to work more closely with our extramural counterparts.

We anticipate a certain number of additional patients will be brought into the clinical center because we're changing some of our recruitment procedures and we're bringing some of the intramural clinical activities that are currently not in the clinical center at NIH into the clinical center. So all of those factors conspired to produce an estimate of roughly 250 beds as the core element.

The extramural advisors felt that we should develop the new Clinical Research Center in a modular fashion, starting with a hospital that was interdigitated with laboratories whose essential missions were so closely linked to hospital activities that it would be a mistake if they were more than one or two minutes away from patient activities. Then there would be a constant, daily interchange between the clinical activities and the laboratory activities.

We carefully examined the existing program, and we identified that we would need roughly 250,000 gross square feet of laboratory space to accommodate those needs. That's where we began. Then we did some comparative benchmarking of what it costs to build such hospitals with ancillary equipment and laboratory space in

roughly 17 other installations. And that gave us an estimate of cost for the proposed project.

CLINICAL RESEARCH CENTER RENEWAL

Mr. PORTER. Does the President's request, reflect that original NIH cost estimate for the hospital, or was it adjusted downward in the course of the budget process?

Dr. VARMUS. It was adjusted downward. The original estimate was \$380 million.

Mr. PORTER. And is this a scaling back of the scope of the facility?

Dr. VARMUS. Well, we believe we can do the essential work with the money that's being requested. Obviously, to give you a precise number for the cost of the building would require a more detailed planning process than we have currently carried out. But we feel confident that within the boundaries of the President's request we can build a research hospital and sufficient laboratory space to handle the crucial elements.

TOTAL COST OF CRC

Mr. PORTER. Now, the overall request is \$310 million, of which \$274 million is requested this fiscal year?

Dr. VARMUS. No.

Mr. PORTER. I take it back.

Dr. VARMUS. That's the increase.

Mr. PORTER. That's the increase?

Dr. VARMUS. Right.

Mr. PORTER. The \$310 million is the whole?

Dr. VARMUS. Yes. You allocated \$23 million last year for a planning process, which we're in the process of now working through. We will be obligating most of that money, this year.

Mr. PORTER. Does the \$310 million include related costs, such as equipment?

Dr. VARMUS. No. Much of the equipment, however, is currently on campus and will be moved from the roughly 800,000 square feet of space that will be vacated in the existing Building 10. So we don't anticipate tremendous equipment costs.

OPTIONS FOR FINANCING CRC

Mr. PORTER. What other options were considered for financing the new clinical center hospital; in particular, what is the 30 year bond financing option that was discussed?

Dr. VARMUS. Well, we have hired a developer Boston Properties, to help us with the overall management of the clinical research center program. One of the first tasks we gave them was to outline for us all the possible means by which we could finance the new building.

We have considered plans ranging from the one you have in front of you; which would finance the building as an appropriation in a single year, to plans that would request the funds through appropriations over several years at different levels or constant levels; to a plan for a bond issuance that would involve a 30 year loan. We also looked at options that would include trying to raise appre-

ciable amounts of money ourselves through a variety of mechanisms.

We were discouraged from the 30 year bond option for a number of reasons. It would require passage of some legislative proposals before we could go through with it. The total cost to the Government would be larger. And it would be an extraordinary event, very unusual in the annals of Government funding. So we felt that the simplest, most efficient, most direct process would be to ask for the money in a single year.

CRC OUTLAYS

Mr. PORTER. Now, the \$310 million is in budget authority, obviously, that would outlay rather slowly because it would take time to build the building.

Dr. VARMUS. Yes.

Mr. PORTER. Can you give us an idea of the outlay stream associated with the \$310 million in budget authority?

Dr. VARMUS. Well, we've tried to prognosticate the outlay over the next several years. And perhaps the most important thing to point out to you is that in 1997, there would be very little outlay from the 1997 appropriation. That is, most of our outlay in 1997 would be money that was appropriated to us in 1996. I can give you the precise numbers for the record, but, for three years, it would be roughly, roughly \$90 million a year in 1998, 1999, 2000, roughly \$25 million in 2001, and a small amount the following year. The project would be finished late in 2001 or early in 2002.

PROJECTED LIFE OF CRC

Mr. PORTER. What is the projected useful life of the new hospital?

Dr. VARMUS. I've been working with a rough number of 50 years. As you know, we've worked with the existing building since 1952. That building, by contemporary standards, looks medieval. Some very major changes have occurred, and I need to explain them to you, Mr. Chairman.

Perhaps the most dramatic is the idea of interstitial construction—that is, providing a separate space for utility functions. This change has revolutionized the operation of laboratories and clinical research units. This means either creating an interstitial space that exists vertically between areas on a floor or horizontal interposition of space between floors, allowing good access to utilities. I have worked in laboratories of both kinds, non-interstitial and interstitial. The difference is dramatic with respect to the efficiency and the cost of renovation and maintenance.

I think it remains to be seen whether similar revolutions will occur in the future. But I think there's every reason to think that the building we're talking about will last for 50 years.

Mr. PORTER. I've taken a lot of time to try to draw out the essence of the proposal and what the clinical center would consist of. And now I want to turn to my colleagues.

Mr. Istook.

BED SPACE IN THE CLINICAL CENTER

Mr. ISTOOK. Thank you, Mr. Chairman.

Let me shift for just a moment from the new center to the existing one. And first, I'm not sure I clearly followed your answer regarding the bed space. As I understand it, the existing institution has 500 beds. The new one has 250. I'm going by the numbers that were expressed in your justification document.

Dr. VARMUS. The building was originally constructed to hold 517 beds. But over the course of the last several years, because patients are in the hospital for shorter periods of time and because we've had some decline in the patient population, we've reduced the number of operating beds to 325.

[CLERK'S NOTE.—Subsequent for the hearing, NIH revised this figure to "500 beds" for the record.]

Mr. ISTOOK. Okay. And has that differential been in the size of the bed space or was the extra space turned into laboratory space?

Dr. VARMUS. Most of that space has been turned into laboratory space or office space. It's been put to other uses.

Mr. ISTOOK. And it's what again, please?

Dr. VARMUS. Three hundred twenty-five.

Mr. ISTOOK. Okay. So you're saying that's a more valid figure for comparison to the 250, is 325 versus 250?

Dr. VARMUS. It is. But there's an important distinction. Because of the configuration of the units, because a psychiatry unit is very different from the cancer unit, just in general design and adjacent utilities, we could not reduce the current size of the hospital to 250 and maintain the same diversity of activity.

So that's one of the ways in which the new arrangement, the new clinical research center, will generate efficiency. We'll have a better configuration of that allocation.

ESSENTIAL MAINTENANCE AND SAFETY

Mr. ISTOOK. Sure. Your budget request also requests \$11.1 million for what you call the essential maintenance and safety program of the existing facility. Part of it, of course, is for compliance with safety requirements. Another part is modern procedures, equipment, facilities and so forth. According to your document, it says this is the minimum investment required for it, not only until the completion of the new CRC, but also for the next 12 to 15 years.

Do you anticipate, even after the completion, in approximately six years in the new center, that you would then still be using bed space in the existing center for an additional six to nine years?

LABORATORY SPACE IN THE CRC

Dr. VARMUS. Let me clarify something, Mr. Istook, that perhaps I didn't make clear initially. The existing clinical center complex has the hospital we've been discussing, and in addition, a large amount of laboratory spaces. Some is close to and some is farther from patient wards. Those laboratories would still remain functional.

Mr. ISTOOK. So you're speaking of utilizing the labs?

Dr. VARMUS. That's correct. All the clinical activities would be moved from the existing clinical center complex, or Building 10, into the new facility when the facility is completed in 2001 or 2002.

Mr. ISTOOK. Now, are you talking about, the new facility would have sufficient lab space to carry forth the lab work that's currently being done in the existing?

Dr. VARMUS. Only a small fraction of it, about 11 percent.

Mr. ISTOOK. So about 89 percent of the lab work would still be done in the existing facilities?

Dr. VARMUS. That's correct.

Mr. ISTOOK. And 11 percent of the lab work would be done in the new facility?

Dr. VARMUS. That's right.

Mr. ISTOOK. Okay. So you're not going to have the same advantage of the adjacency of the labs to the beds in the clinic?

Dr. VARMUS. There are two factors here, Mr. Istook. First of all, we recognize that not all of the research that goes on in this vast clinical center complex requires close contact with patients. Only a subset does. Furthermore, those investigators who need some patient contact will not be very far removed, because the new facility will in fact be not far from, connected to the old Building 10.

Mr. ISTOOK. What's the distance?

Dr. VARMUS. All of the laboratories within the new center will be within 300 feet of hospital beds. So that will be a one minute transit time. Basically, the patients' rooms are part of the laboratories. The remaining laboratories will be within several hundred feet, often requiring some elevator time. It would not be difficult, for example, to go to the patient ward to receive one sample a day.

Mr. ISTOOK. The labs which represent the 11 percent of the labs that would be a part of the new center—

Dr. VARMUS. That's correct.

Mr. ISTOOK [continuing]. Those what you're saying would be within 300 feet?

Dr. VARMUS. That's right.

Mr. ISTOOK. Those which would comprise 89 percent of the labs would be what distance? I'm not clear on that.

Dr. VARMUS. Would take a few minutes—

Mr. ISTOOK. What is where?

Dr. VARMUS. The remaining laboratories would be in the 14 story building, the existing Building 10, and would be anywhere from a few minutes to perhaps 10 minutes away from the patient depending on elevator transit time and the distance.

Mr. ISTOOK. What's the horizontal distance?

Dr. VARMUS. It could be anywhere from a few hundred feet to as much as a quarter of a mile.

Mr. ISTOOK. Okay, so you're talking about the two end points, the farthest end points of the two buildings would be a quarter mile?

Dr. VARMUS. Roughly correct, I believe. I haven't measured it precisely.

FUNDING FOR SAFETY REQUIREMENTS

Mr. ISTOOK. Of the portion of the \$11.1 million, some of it you say is for safety requirements. The other is for, what you called the

modern procedures, equipment, facilities. How much of that is the safety component? Do you have a workup on that?

Dr. VARMUS. We reduced that budget this year, as you've seen, trying to constrain the budget in every way to make money available for grants.

Mr. ISTOOK. Right.

Dr. VARMUS. But perhaps you want to speak to Mr. Ficca.

Mr. FICCA. Actually all of it is, the equipment that they're referring to is the equipment that directly relates to the facilities infrastructure, the utility system. This is the fourth year of a four-year program. This will be the last increment. And it is to replace the dynamic air handling systems of the existing Building 10, the original core.

Mr. ISTOOK. So how much are you saying is the safety component?

Mr. FICCA. The entire project is addressed at the safety of the existing facility. So it all is, even though it says equipment, it's equipment that relates directly to air handling equipment that is required. Right now, the existing facility is deficient by about 50 percent in its air handling capacity. And this causes fume hoods not to work, there's a moratorium on fume hoods and other scientific equipment.

Mr. ISTOOK. Okay, so really, you're saying the entirety of the \$11.1 million is considered to be a safety component because it relates to the air handling system—

Mr. FICCA. That's correct.

Mr. ISTOOK [continuing]. Which especially, because of the fumes that are generated—

Mr. FICCA. That's one of them—

Mr. ISTOOK [continuing]. Needs to be upgraded.

Mr. FICCA. Yes.

SAFETY STANDARDS

Mr. ISTOOK. You have a moratorium on that currently. And is there, what standard do you apply? Who develops the standard that you utilize on those safety requirements?

Mr. FICCA. There's several standards. But there's been four independent studies that have been done by laboratory and hospital consultants, engineering consultants.

Mr. ISTOOK. Which standards did they apply?

Mr. FICCA. That has to do with the number of air changes that are required in certain—I'm not sure, I'd have to supply that for the record, it could be, it's called American Society of Heating Refrigerating and Air Conditioning Engineers.

Mr. ISTOOK. Yes, and I know there's different groups that set those. I'm just wanting to understand who sets the standards that you follow here, whether it's something that's set by a Federal Government entity, whether it be internal to NIH or the Occupational Safety and Health Administration or an outside group, whoever it might be.

Mr. FICCA. We do comply with all of those. That's one of the drivers of the program, is the environmental and occupational safety and health policies and standards.

Mr. ISTOOK. If you could get that information to us.

Mr. FICCA. I will supply that.

Mr. ISTOOK. We would appreciate it.

[The information follows:]

VENTILATION SYSTEMS DESIGN STANDARDS

The following standards are followed in the evaluation and design of ventilating systems:

Federal

Occupational Safety and Health Standards (OSHA), CFR 29, Part 1910.

Guide for the Care and Use of Laboratory Animals, U.S. Department of Health and Human Services.

Non-Federal

Building Officials and Code Administration (BOCA).

American Society of Heating, Refrigerating, and Air Conditioning Engineers, Inc. (ASHRAE).

Industrial Ventilation: Manual of Standard Practice.

Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry, National Sanitation Foundation Joint Committee on Biohazard Cabinetry.

National Fire Codes, National Fire Protection Association.

American Society of Hospital Engineering.

REPROGRAMMING FOR ROUND ROBIN PROGRAM

Mr. ISTOOK. The building account, at the beginning of fiscal year 1996, you had an unobligated balance of approximately \$141 million. I'm not sure from your indication here whether you expect the unobligated balance at the end of fiscal year 1996 to be zero or you are just saying that we don't know at this point.

Dr. VARMUS. Much of that unobligated balance is designated for a building that's a component of a different construction project called the Round Robin Project.

Mr. ISTOOK. Sure.

Dr. VARMUS. And we're coming forward to the Department in the very near future, then subsequently to the committee, with a reprogramming request for the construction of the final phase of that project.

Mr. ISTOOK. You say a reprogramming request. Reprogram it from what to that project?

Dr. VARMUS. It's from a number of previously indicated projects, including a request to build a second phase of the Natcher Building, an administrative building, on the Bethesda campus that we have decided not to expand, and a building for animal care that was going to be constructed in Poolesville that we no longer need.

Amalgamations of those allocations, along with money from the original Round Robin program will be put together to constitute roughly a \$90 million fund for constructing the last phase of the laboratory Round Robin. This is to replace some of the buildings that were constructed in the 1930s that are antiquated and no longer safe or functional for laboratory use.

Mr. ISTOOK. Okay. And this is laboratories for which component of NIH?

Dr. VARMUS. It's for several institutes. It would actually be housing some of their investigators in this new component.

UNOBLIGATED BALANCES

Mr. ISTOOK. And again, trying to understand, as the Chairman was asking, about anticipated outlays, do you anticipate at the end of fiscal year 1996 that there would be no unobligated balance, that there would be some number or what? Presuming that reprogramming was——

Mr. FICCA. The budget document, as you indicate, indicates nothing there for an unobligated balance. Our goal would be, of course, that that would be the case. But each year there always tends to be. We would anticipate some small unobligated balance. But those unobligated balances are funds that have been appropriated for particular projects. They are committed to particular projects. It is usually a question of the procurement process running its course in order that we can fully obligate those programs.

Mr. ISTOOK. Sure. And there's an open question, of course, I would think, on whether any portion of the unobligated balance should be applied towards the needs that you've been requesting. I don't know the relative priorities of the projects, whether it be the Round Robin or the clinical care.

But I think it would be very important to all the members of the committee to have a full understanding of what you intend to do or desire to do with the \$141 million that's unobligated, so that we can put that into this entire equation that we're looking at. And certainly, detailed information on that would be very important to have.

[The information follows:]

UNOBLIGATED BALANCES

The \$141,510,000 unobligated balance includes approximately \$128,000,000 that is committed for projects that address essential safety and health improvements and regulatory requirements for the NIH buildings and facilities. Included in this amount is approximately \$55,000,000 that has been identified for a pending reprogramming request to complete construction of the Consolidated Laboratory Building (Building 50). Of the remaining, approximately \$7,200,000 is committed for building closeouts and claims, and approximately \$6,300,000 is committed to maintenance and repair projects within the B&F Repair and Improvement Program.

In what you mentioned with the Round Robin, Dr. Varmus, and the laboratory space for different components, different institutes, what would that mean through that project and the one you're requesting here? What then would be the oldest remaining and utilized lab space within your campus?

Dr. VARMUS. The oldest would probably be the laboratory space to be renovated in Building 6, for which there is some money requested for some renovations. The next oldest would probably be the laboratory space in the clinical center complex in Building 10, which is 1952.

Mr. ISTOOK. So the lab space is older in——

Dr. VARMUS. Building six has two components that are old and new.

Mr. FICCA. The original Building 6 is of the same generation as the——

Dr. VARMUS. Built in the late 1940s, I believe, I don't know the precise year, but I can find that out for you.

[The information follows:]

BUILDING 6

Construction of Building 6 was completed and the facility occupied in September 1939.

REPLACEMENT SQUARE FOOTAGE

Mr. ISTOOK. And the Round Robin lab space that you were describing, that's replacement space or additional space?

Dr. VARMUS. That's replacement space.

Mr. ISTOOK. That's replacement. Okay. And what's the—I realize square foot is not your only—

Dr. VARMUS. That's all right. It's roughly 300,000 gross square feet (GSF).

[CLERK'S NOTE.—Subsequent to the hearing, NIH changed this figure to "250,000" for the record]

Mr. ISTOOK. Compared to what size of space that it would be replacing?

Dr. VARMUS. There's about a 20 percent increase in space.

Mr. ISTOOK. So that Round Robin would be a 20 percent increase in space for the space that it's replacing. And square footage wise, between the new clinical center and the 89 percent or whatever that would remain in the existing center, what's the differential on the existing versus—

Dr. VARMUS. Actually, there's a loss of space in that setting, Mr. Istook. Because the new clinical research center would have about 850,000 square feet gross. It leaves behind about 800,000 square feet gross. But when the renovations are done, and we appropriately refit Building 10 to meet adequate standards, the amount of usable space will decrease.

Mr. ISTOOK. That's factoring in Building 10.

Dr. VARMUS. Well, Building 10 is the appropriate comparison, because you're asking how much—

CLINICAL RESEARCH CENTER RENEWAL

Mr. ISTOOK. Is Building 10 the existing clinical center?

Dr. VARMUS. Yes, the Clinical Center complex. I should also say that when we talk about an increase in the Round Robin, those comparisons are not entirely fair. I know it's convenient for us to make them, because square footage is useful.

But if you would visit the existing laboratories, you would see that they are labyrinthine and a series of cubbyholes. It's very inefficient space. People are crammed in there in a way that really is not very humane. So we can generate much more usable space. There will be some decompression that will make the whole place safer and more pleasant.

Mr. ISTOOK. The portion that's in Building 10, in the existing clinical center, that's bed space, the 325 beds, did you indicate you planned to convert that to lab space?

Dr. VARMUS. Ultimately.

Mr. ISTOOK. Ultimately. That's a separate venture?

Dr. VARMUS. The external advisors said we should defer deciding exactly what to do with that, although we should make some general plan until more time has gone by and we have evaluated how the intramural program is progressing, what the status of biomedical research is in the country, what the fiscal fate of the NIH

and the country might be. So all these factors can be taken into consideration some years from now.

ROUND ROBIN PROGRAM

Mr. ISTOOK. Would remodeling it for that purpose satisfy the needs of the Round Robin program?

Dr. VARMUS. Well, we couldn't do that until at least seven or eight years from now.

Mr. ISTOOK. If you just looked at the square footage as opposed to looking at the time frame, would it—

Dr. VARMUS. Square footage would be fairly close, I think.

Mr. FICCA. The existing, the laboratory space that would be remaining in the old building, once the CRC is occupied, would pretty much be used up in the time frame that we're talking about by the year 2000. In other words, there would be no space in a renovated Building 10 to be able to address the needs in the Clinical Center and the Round Robin. The Round Robin laboratory spaces that are being replaced are Buildings 2, 3, 6 and 7.

Mr. ISTOOK. Yes, but when you say it would be used up, again, you're talking about the time frame difference, that before you can anticipate—

Dr. VARMUS. Well, strictly speaking, Mr. Istook, your point is well taken. But I don't believe it would be appropriate to try to use the buildings that are part of the Round Robin for another 10 years. The other point I would draw your attention to is the fact—

Mr. ISTOOK. Let me understand. When you say it would not be appropriate to use the buildings that are part of the Round Robin for another 10 years—

Dr. VARMUS. The buildings that we are trying to vacate.

Mr. ISTOOK. You're saying the Round Robin would not become on line, so to speak, for 10 years, or what do you mean?

Dr. VARMUS. Yes. We can't begin to renovate the hospital space that we're going to vacate until we finish the clinical research center—

Mr. ISTOOK. Right.

Dr. VARMUS [continuing]. Until 2002.

Mr. ISTOOK. Until the new center is built and you could then—

Dr. VARMUS. By the time we did those renovations, it would be at least 2005, and perhaps longer.

Mr. ISTOOK. Sure. Whereas the Round Robin construction program would have those facilities—

Dr. VARMUS. We can have those in 1999.

The other point I would draw your attention to is something we haven't discussed so far. But your question leads me to mention it, and that is that we do have a number of laboratories in the intramural program that are on off campus sites. We are currently paying quite a bit of rent for some of those places. Good research is done there, but I'm concerned about the isolation of those scientists from the mainstream activities on the Bethesda campus.

The one potential considerable savings that would result from the ultimate renovation of the existing patient space in Building 10 would be to bring some of those programs back to the campus. Now, that's one of the things I think that needs to be factored in

some years from now, when we're in a position to reevaluate the program more thoroughly.

Mr. ISTOOK. Okay. I want to explore some more, but I need to pass right now on my time.

Mr. PORTER. Thank you, Mr. Istook.

Mr. Riggs.

PATIENT CARE DAYS

Mr. RIGGS. Thank you, Mr. Chairman.

Dr. Varmus, good afternoon. One thing I should have asked earlier, just for my own edification, because I have not had the opportunity to visit the campus, which I would very much like to do.

Dr. VARMUS. We hope to give that to you sometime in the middle of May.

Mr. RIGGS. To be honest with you, sir, I had intended to do that prior to now. That is to say that, the beginning of the 1997 appropriations process. So I apologize, I have not done that, and would like to do it.

One thing I'm not clear on, though, as a lay person, is with respect to the clinical center, what—let me back up for a moment. Is this all in-patient care, or is a portion of it out-patient care? And what is the percentage breakdown?

Dr. VARMUS. I'm going to ask Dr. Gallin, who's in charge of it, to give you the precise numbers.

But the answer to your question, in simple form, is that there are three components. There is out-patient care, of which there is a considerable amount. There is patient care, which is delivered to patients who come into the hospital for the day, to receive some kind of research attention, and then sleep somewhere else. And then there are roughly 200 patient beds for patients who are resident in the hospital.

I'll ask John Gallin to comment on the precise numbers.

Mr. RIGGS. Please.

Dr. GALLIN. We have approximately 63,000 in-patient days per year, and about 79,000 out-patient visits. That was projected for this year. And of those out-patient visits, about 12,000 are in the day hospital sites.

Mr. RIGGS. And would one of those day hospital sites be Stanford University in our part of the world?

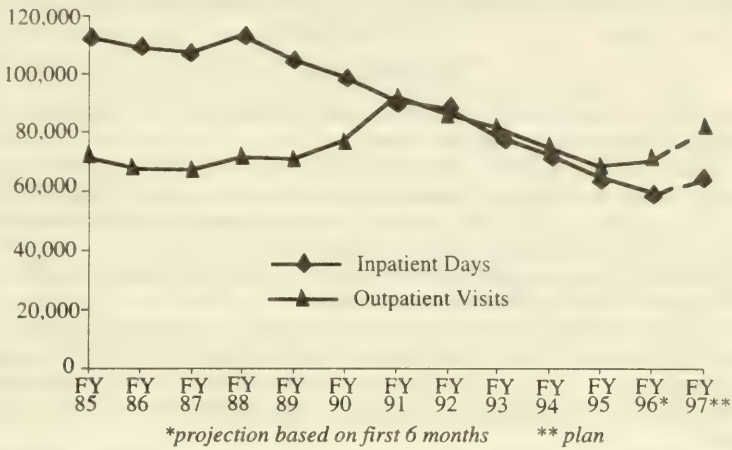
Dr. VARMUS. No, these are all visits occurring at the clinical center in Bethesda. I might further embroider Dr. Gallin's answer by pointing out that that's roughly half, nearly half of all the patient days or patient nights for clinical research activities in the entire country, and about one-fourth of all research-oriented out-patient visits throughout the country. So we're talking about a very large center that does an extremely large fraction of all the patient-oriented research in the country.

Mr. RIGGS. I see. And has your patient load been steady, been increasing or been decreasing?

Dr. VARMUS. In-patient census has been gradually declining over the last several years. We are anticipating some reversals of that trend for a number of reasons. This is a brief chart that would illustrate that for you.

[The information follows:]

Clinical Center Patient Activity (FY85 - FY97)



But we're anticipating a number of changes, returning some of our intramural research activities from outlying sites to the clinical center and creating new ways for the extramural research community to interact with us, for example, bringing some of their patients to our clinical center for use of specialized equipment and for access to our specialized scientific activities.

PATIENT CARE

Mr. RIGGS. And the in-patient care, would it be properly categorized as acute care, critical care?

Dr. VARMUS. It is all research care. Some of the patients are acutely ill. For example, those patients who come to the clinical center with advanced AIDS or with cancers that are far advanced. Those patients, of course, have very acute care.

Mr. RIGGS. What percentage of your patients, are terminal?

Dr. GALLIN. We had 54 deaths last year.

Dr. VARMUS. There are also patients who are not acutely ill, but come to the clinical center regularly, for evaluation of the progress of the disease, or are in long-term protocols for the treatment of rare diseases, for example, for whom this institution is the grand resource.

Mr. RIGGS. And with the building of the new clinical center, how would your capacity or projected patient load increase?

PATIENT CARE CAPACITY

Dr. VARMUS. Well, we think the patient load would not increase dramatically, but it would be handled much more efficiently, because we would have a much higher occupancy rate. I should explain that in a research hospital, the daily census is not uniform throughout the week or the year. So we have a peak census, usually on Wednesdays. On the weekends, the census is somewhat lower, because patients who are well don't need to be hospitalized on the weekends, when the research activities are at a low ebb.

Similarly, during the holiday periods, we don't arrange for our research patients elsewhere in the country to come in electively, for follow up care of a chronic illness or hereditary illness. Our peak census is around 210. But that is true in the middle of the week, in our active seasons. So it's not like an ordinary hospital in that sense.

Mr. RIGGS. It sounds like the great degree of your patients are ambulatory, in fact?

Dr. VARMUS. I would say the majority are ambulatory. Is that fair, John?

Dr. GALLIN. Yes.

SQUARE FOOT COST OF CRC

Mr. RIGGS. Now, the Chairman asked you a little earlier about the per square foot cost of constructing the new clinical center. What is that cost, fully equipped with all items, assuming all the latest diagnostic and treatment?

Dr. VARMUS. Well, much of the equipment will not be required to be purchased, it will be moved from the old hospital. To establish the estimates, we have compared 17 other institutions of simi-

lar quality and activity. And we have generated a number which is more or less the average for those 17 institutions.

The number per square foot Mr. Ficca estimates to be around \$370 per square foot.

Mr. RIGGS. I was going to estimate somewhere in the neighborhood of \$300 to \$400 a square foot.

Dr. VARMUS. You and I are from California. [Laughter.]

Mr. RIGGS. Have you actually put this project out to bid?

Dr. VARMUS. For construction bid, no. We have, as I mentioned earlier, hired Boston Properties to do the management of the entire project. They will be the focal point for responsibility, for letting the contracts, for construction, and for helping us to manage all other aspects of the program.

We have also had a design concept competition, in which selected architectural firms were finalists, and reviewed by both scientists and outside architects. The firm called Zimmer-Gunsul-Frasca, ZGF, from Portland, Oregon, a firm that is known to many of us because of its activities in biomedical and hospital construction, has been selected as the architect.

EFFECT OF FULL FUNDING

Mr. RIGGS. I guess my last question would be, and I think the Chairman may have asked you this the other day, in your testimony, you're looking for full funding?

Dr. VARMUS. That's correct, we're asking for full funding in fiscal year 1997.

Mr. RIGGS. Will that affect your budget request in any other area of your budget, that is to say, I mean, will you—

Dr. VARMUS. Yes, sir, it does. In the sense that the large request for the construction, has influenced the design of our budget proposal. We are trying to generate as much money as possible for research project grants, the investigator-initiated awards that we believe to be our highest priority programmatically. So we are holding virtually everything else in the NIH budget at a basically flat 1996 determined position in order to generate new grants and maintain an adequate success rate for our grantee applicants.

Mr. RIGGS. And in order to be able to get the funding, you hope, the full funding, for construction of the new clinical center.

Dr. VARMUS. Well, it's partially in response to the significant portion of our increase that would be devoted to the construction project.

Mr. RIGGS. I see. Okay.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Riggs.

LENGTH OF CRC CONSTRUCTION

Mr. Wicker.

Mr. WICKER. Dr. Varmus.

Dr. VARMUS. Mr. Wicker.

Mr. WICKER. This clinical research facility takes six years to construct?

Dr. VARMUS. The construction would begin in 1998 and would conclude by the end of 2001, or the start of 2002. It's approximately right.

Mr. WICKER. Okay. And it's got a proposed useful life of 50 years or more?

Dr. VARMUS. Hopefully more.

FUNDING THROUGH BONDS

Mr. WICKER. I'm intrigued by the question the Chairman asked about 30 year bonds. And I wonder if you could be more specific about why you recommend against that proposal. Did you state that this would be more costly?

Dr. VARMUS. It would be more costly.

Mr. WICKER. How so?

Dr. VARMUS. Because we would have to pay interest on the loan. The total cost would be roughly \$680 million, based on a \$380 million project.

[CLERK'S NOTE.—Subsequent to the hearing, NIH corrected this figure "\$800 million" for the record]

Mr. FICCA. It would be about 60 base points. If the bond would be issued, it would probably be about 60 base points above the current Treasury rate, whereas of course if you use Federal funds, it would be almost \$25 million to \$30 million over 30 years. So the total cost from that standpoint would be more.

Dr. VARMUS. It's about \$800 million in 1996 dollars.

Mr. WICKER. Okay. Do you have specifics on that that you can furnish to my office?

Dr. VARMUS. Yes, we do.

[The information follows:]

BOND FINANCING

Government secured bond financing would be approximately 60 basis points above the 30 year Treasury Note. This would result in an annual payment of approximately \$26 million over 30 years for a total cost of \$780 million based on a principal amount of \$320 million. The net present value of this funding mechanism is \$282 million.

The NIH had investigated commercializing certain of its assets to generate revenues to offset the bond financing. This would include revenues derived from paid visitor parking, leasing authority, leased retail spaces, intellectual assets, third party collection, and gift fund raising. This method was not selected because of the complexity to administer and the uncertainty of securing special authorizations needed to fully implement this option.

Mr. WICKER. Okay. What would have been the annual payment on the 30-year bond?

Dr. VARMUS. Between \$25 million and \$30 million.

Mr. WICKER. Okay, well, I would certainly like to see some information on that.

Dr. VARMUS. There would also be the need for some legislative proposals to be passed. It would take us a couple of years to get the program going.

Mr. WICKER. So it would delay the program?

Dr. VARMUS. It would delay the program.

INCREASES IN B&F FUNDING LEVELS

Mr. WICKER. Okay. Now, I see that your building and facilities funding levels have increased by about 50 percent over the last five years. Fiscal year 1992, \$101 million—is that correct?

Dr. VARMUS. I think I would not characterize it quite that way, Mr. Wicker. Last year was a higher year than usual. But there were two things in that proposal that are unusual. One is the \$23 million for planning for the clinical research center. And the other was the final appropriation for the end of the Round Robin, the consolidated laboratory building.

Mr. WICKER. Okay. So the big jump was——

Dr. VARMUS. For special projects. If you look at the essential maintenance and safety aspects, and other minor items, I think you'd find that the expenses actually are rather low. Especially if you view it in relation to the size of the intramural research program. It's really quite economical.

EFFECT OF CRC ON FUTURE REQUESTS

Mr. WICKER. Could you speculate as to the effect of this new clinical research center on your future requests, say over the next five years?

Dr. VARMUS. I think there's every reason to believe that it will reduce them, since we can vacate part of the existing clinical center and much of the essential maintenance and safety requirements will be diminished. Moving our patients out of that building will help tremendously.

Mr. WICKER. Okay. Have you——

Dr. VARMUS. Unless, of course, we decide at some future date to enter into a period of renovation of that space. But that would not happen until after we completed the new building.

Mr. RIGGS. He qualified it. [Laughter.]

CRC BOARD OF GOVERNORS

Mr. WICKER. Let me just ask you about these series of NIH committees which have, which currently run the NIH clinical center. Do you consider that setup to be a problem in terms of managing the facility?

Dr. VARMUS. I'm not sure what committees you're referring to, Mr. Wicker.

Mr. WICKER. Well, let me find it in the testimony, then. Do you have a proposal for a new——

Dr. VARMUS. Are you referring to the Board of Governors? The Smits Report, which was produced by an options team organized by the Secretary, has recommended that we develop what is standard practice in academic hospitals, a Board of Governors composed in part of intramural clinical scientists, in part of individuals on the outside, often hospital administrators and other public members. The board will report to me and oversee the activities of Dr. Gallin, the Director of the Clinical Center. It will look at the management of the Clinical Center, not at the scientific activities that are conducted there. Let me point out that the scientific activities that go on in the clinical research center are directed by roughly a dozen or so institutes and centers that have scientific programs with patient-oriented components.

But management is an area where the Smits Committee felt that we could be more efficient. They especially felt that we should have a Board of Governors that oversees the management issues and that we need a more stable funding base for the clinical center. The

clinical center, you will recall, does not have its own line in the appropriations process, but instead is recompensed through monies that are received from the individual institutes in accord with their use of the clinical center.

It was also recommended that we develop new efficiencies through government reinvention programs, that we develop ways to generate some income for the clinical center through use of third party payors, and that we develop means for no-year money for the clinical center to help with operations.

So there are a number of recommendations, many of which would be overseen by the new Board of Governors. Names of Prospective Board Members have been submitted to the Secretary. We expect to have the board in place very soon. The Smits Report was only delivered to us a few months ago. We are quite enthusiastic about having a governance that is more responsive to current changes in health care, and takes advantage of efficiencies that have been achieved in the academic sector over the last several years.

Mr. WICKER. Thank you, Mr. Chairman.

COST OF A&E STUDIES

Mr. PORTER. Thank you, Mr. Wicker.

Dr. Varmus, the 1996 appropriation bill provided for \$23 million for detailed architectural and engineering plans for the hospital. Is that the typical market price for an analysis of this kind, and when will the plans be completed?

Dr. VARMUS. Whether it's a typical price or not, I can't tell you. But the plans will be completed in roughly 15 months. I can tell you that the money is being obligated in this year. What we're asking for is a schematic design and development of the architectural plan. I would have to supply for the record what such a plan would normally cost in the private sector.

[The information follows:]

DESIGN FEES

The normal fees for designing healthcare facilities and research laboratories in the private sector are in the range of 8.5% and 14% of the construction costs as established by an independent national survey conducted in 1996 by PSMJ Resources, Inc. The FY 1996 request of \$23 million includes design fees of \$19 million for detailed programming through the design development stage and associated management fees of \$4 million for the Development Manager, Construction Manager, and Government. The total estimated design fees for \$36.5 million for the Clinical Research Center project is 11.3% of the estimated construction cost, which is well within the industry standard range.

DESIGN OF CRC

Mr. PORTER. What does the design look like? Do you have a rendering?

Dr. VARMUS. I do, and I could refer you to a recent issue of Architecture magazine, which—I'm sorry we didn't bring today, because it reviewed the design competition. A member of the editorial staff of Architecture magazine was on the review committee.

I can describe it for you very briefly. The winning proposal recommended four relatively low-lying, four story brick buildings, modest in appearance and scope, highly functional in design. If you've ever been to the Fred Hutchison Cancer Center in Seattle

or to the Vellum Institute in Portland Oregon, you will have seen very similar buildings.

The buildings will fit in very well in the site that's proposed. They will neither be dwarfed by nor interfere with the current view of the clinical center. They will incorporate very nicely the ugly "flash cube", that's often the term used to refer to the existing ambulatory care center. It will turn the base of the flash cube into a plaza that will provide at least some congregation space that is sorely missing on the NIH campus.

So it has many attractive features. It is, in my view, the kind of design that will be economical and efficient for the kinds of use to which we're going to be putting it.

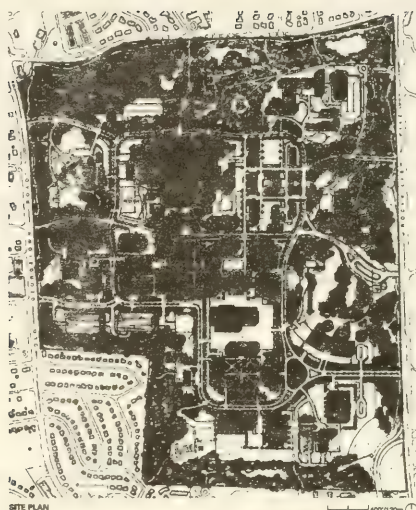
Representatives of the neighborhood have also looked at the design, and they're very enthusiastic about it. We can show you these very poor xeroxes, but I prefer to send you a copy of Architecture magazine.

[The information follows:]

CLINICAL RESEARCH CENTER DESIGN

Copy of Architectural Magazine Attached

Competition



NIH's Newest Experiment

The National Institutes of Health selects an architect to expand its Clinical Center through a design competition.

The gospel of the General Services Administration's Design Excellence Program is finally winning converts in other federal agencies. Last fall, the National Institutes of Health (NIH), the government's nerve center for biomedical research, staged a landmark competition to design a \$380 million clinical research center on its 322-acre wooded campus in Bethesda, Maryland. The proposed 850,000-square-foot facility will be part hospital and part laboratory, a high-tech hybrid for the next century. "It's going to be an important center," asserts John I. Gallin, NIH's associate director of clinical research, "not just for the NIH, but for the country and the whole biomedical community."

The plan is to place 250 inpatient beds and 100 outpatient stations right next to clinical research labs and treatment areas. The new building will adjoin and replace outdated, overcrowded space within the NIH Clinical Center's 19-story building, the tallest on campus. Completed in 1952, the brick-clad tower known as Building

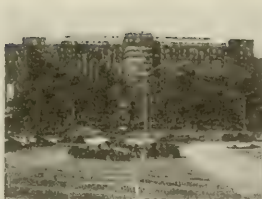
10 sprouts the Ambulatory Care Research Facility (ACRF), a 1 million-square-foot glazed box nicknamed the "flash cube." Together, the two buildings make up the 3 million-square-foot Clinical Center Complex, the nucleus of the NIH campus.

Staked out on 45 acres in 1935 under President Franklin D. Roosevelt, the grounds originally comprised three Georgian-style buildings arrayed around a quadrangle. Today, 70 buildings are informally scattered over the

TOP LEFT: Campus master plan shows placement of proposed addition to north of clinical complex (top).



NEO-CLASSICISM: Original NIH building



CLINICAL CENTER: Proposed by Skidmore, Owings & Merrill



CLINICAL CENTER: Proposed by Kohn Pedersen Fox Associates

rolling, tree-lined landscape set within a suburban residential neighborhood. New buildings must conform to a 1993 master plan devised by local architects Oudens and Knapp with Keyes Condon Fierman.

Architect Walter Armstrong of NIH's Division of Engineering Services fashioned an unusual protocol for awarding this enormous project, adopting the two-stage Design Excellence selection process piloted at the GSA by Chief Architect Edward Feiner in 1994. The NIH was able to select its architect outside the writ of the federal Brooks Act by signing a contract with Boston Properties, a private developer that has realized projects for other government agencies, to package financing, conduct the competition, and oversee design and construction.

The competition turned out to be like a large-scale laboratory experiment. It left some contenders doubting the efficacy of the GSA's new tangled selection process for such a technically sophisticated building. "The program is a very poor substitute for face-to-face conversation," laments one shortlisted candidate. "And when an agency hires a project developer who says, 'Please don't speak with the client,' you can guess they don't have a real interest in architecture."

Twenty-nine firms responded to the *Commerce Business Daily* solicitation last July. All were screened by a team of NIH architects and engineers, Boston Properties senior vice presidents Robert Burke and E. Mitchell Norville, and a group of professional advisors: the GSA's Feiner, Deborah Dietsch, editor-in-chief of *ARCHITECTURE*; Roger Montgomery, former dean of architecture at the University of California, Berkeley; and Jules Levine, associate vice president of health sciences at the University of Virginia.

The initial screening evaluated each firm's past design performance and philosophy, as well as the lead designer's portfolio. A few emerging firms such as Morphosis were considered, but the panel concluded that less-

established firms could not handle the project's programmatic and technical complexity.

The preliminary group was winnowed to a shortlist of six candidates: Kohn Pedersen Fox (KPF) with Hansen Lind Meyer, Kaimann McKinnell & Wood Architects (KMW), Cesar Pelli & Associates; Renzo Piano Building Workshop; Venturi, Scott Brown and Associates (VSB), with Payette Associates; and Zimmer Gunsul Frasca Partnership (ZGF).

The shortlisted firms were given a stipend of \$50,000 and four weeks to assemble teams, devise a scheme, and prepare presentation boards. The presentations were publicly exhibited at NIH, where staff were encouraged to comment. The competitors were evaluated on the basis of team organization and design, each half of the total score.

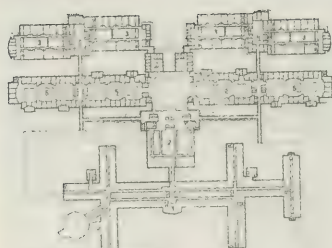
Each team was interviewed and rated by Boston Properties and a panel of NIH personnel: John Gallin, associate director of clinical research; Michael Gottesman, deputy director of intramural research; Gregory Curt, clinical director of the National Cancer Institute; and Robert Nussenblatt, scientific director of the National Eye Institute, as well as Project Manager Walter Armstrong; George Williams, director of special projects; and Janet Hedetniemi, the agency's community liaison. Nonvoting advisors Feiner, Dietsch, and Montgomery also attended.

Program criteria stipulated 11-by-33-foot lab modules, maximum 400-foot distances from patient units to laboratories, 18-foot floor-to-ceiling heights (incorporating interstitial floors), flexible spaces and infrastructure, efficient stacking, and clear circulation. Schemes were also rated for esthetics and contextual response. Because the new building will mediate between the campus and surrounding neighborhood, scale became a key factor. "Our master plan was carefully crafted with community involvement," explains Hedetniemi. "We were concerned about visual impact and the need for openness and accessibility to our community."

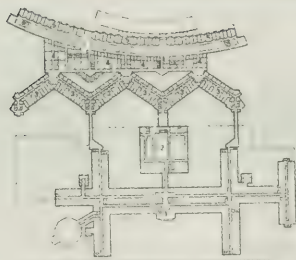
Most firms, however, proposed monumental massing and expansive footprints that appeared more like a hospital than a campus building. The two firms rated highest, ZGF and KMW, were reinterviewed by the panel and by NIH Director and Nobel laureate Harold Varmus. ZGF won the competition based on its past experience, team of consultants, and a design scaled appropriately to the campus and flexible enough to accommodate future needs. "We preferred modest over monumental," explains Gottesman.

In contrast, Pelli, ranked last overall, proposed a 170-foot-high curved wall fronting the wooded campus entrance. Piano, who assembled an impressive team and wowed the panel with an eloquent, persuasive argument, presented a similarly monumental scheme. The panel appreciated KPF's striking plan, which would have relocated the axial entrance to the complex and integrated natural elements—vegetation and daylight—into the clinical realm, but it had the largest footprint and was deemed functionally inefficient. The approach by VSB/Payette was judged the most efficient, but its brick elevations struck the panel as reminiscent of public housing.

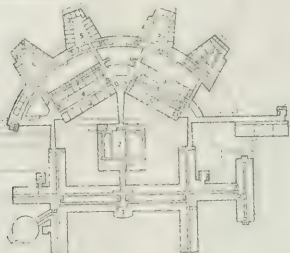
While the NIH competition yielded a provocative range of results, questions were raised over whether this type of competition was well suited to such a complex project. The design teams were given general program information, afforded minimal interaction with the client, and were thus left to devise sketchy responses. Most of the architects construed NIH's quest for a pace-setting, landmark facility—akin to Louis Kahn's Salk Institute—as a call for a monumental building rather than a recessive campus structure. Yet "the building could have been high-rise or low-rise; the client didn't know what it wanted," reports the GSA's Feiner. "Only when the proposals were made could the NIH see what the ramifications would be. But all the architects had the same information: the site is no mystery." —Bradford McKee



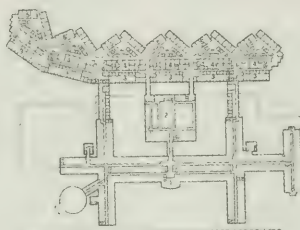
ZIMMER GUNSUL FRASCA PARTNERSHIP



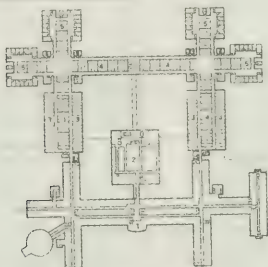
KAIL MACKINCKELL & WOODCOCKMORE OWINGS & MENDEL



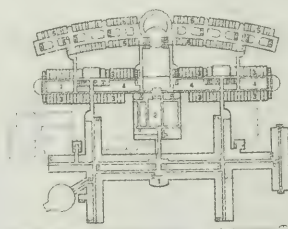
KOHRS PETERSEN FOX HANSEN LIND MEYER



VICTOR SCOTT BROWN AND ASSOCIATES/PAVITT ASSOCIATES

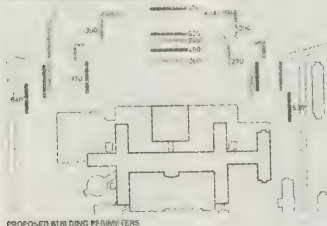


RENZO PIANO BUILDING WORKSHOP



CESAR PELLI & ASSOCIATES/HKS/LED A DALY

1. MEDICAL CENTER BUILDING/10
2. AMBULATORY CARE/RESEARCH FACILITY
3. LAB BLOCK
4. SUPPORT AREAS
5. PATIENT CARE KITCHEN



PROPOSED BUILDING PERIMETERS



PROPOSED BUILDING HEIGHTS

- | | |
|------------|------------|
| 100' PIANO | 100' PIANO |
| 150' PIANO | 150' PIANO |
| 150' PIANO | 150' PIANO |
| 150' PIANO | 150' PIANO |



ZIMMER GUNDEL FRASCA

PARTNERSHIP

Design Ranking: 1

Technical Ranking: 1

Final Ranking: 1

Zimmer Gunsul Frasca's quiet, four-story complex mediates between the 10-story Clinical Center Complex and ancillary structures at the campus edge. The widest and lowest of the proposed schemes, brick buildings paired around courtyards blend with the Clinical Center tower, the original swirl quadrangle, and adjoining neighborhoods. "The building fits like a glove on the campus," asserts Project Manager Wade Armstrong.

The scheme comprises two parallel east-west wings, flanking the main circulation and interaction space. The blocks are arranged to house either labs or patient care units. "I liked the design because it was so flexible—we could put a lab in a patient room or a patient in a lab space," remarks Associate Director of Clinical Research John Gailim.

Within the patient blocks, 10 flexible patient care units hold 35 beds each, while nursing stations serve quadrangles to bed clusters. Top floors of each patient wing contain sunrooms and outdoor terraces, and pedestrian bridges on the eastern and western ends connect to the complex.

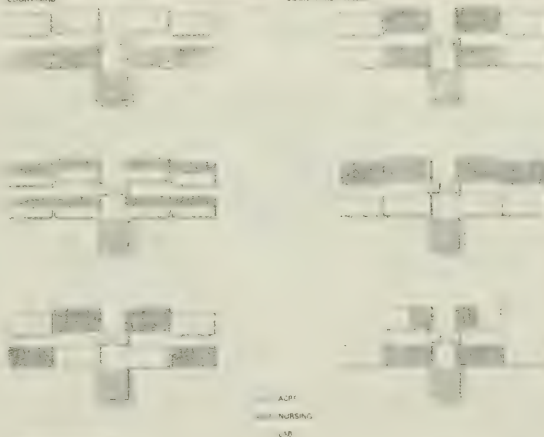
The selection panel liked how the architects proposed to wrap the existing glass-clad Ambulatory Care Research Facility in brick, with a new core of elevators and lobby. The new glass podium crowning the atrium was deemed ungainly, but during the interview, ZGF noted that it could be replaced by a drum, barrel vault, or cone.



COURTYARD



COURTYARD ATRIUM

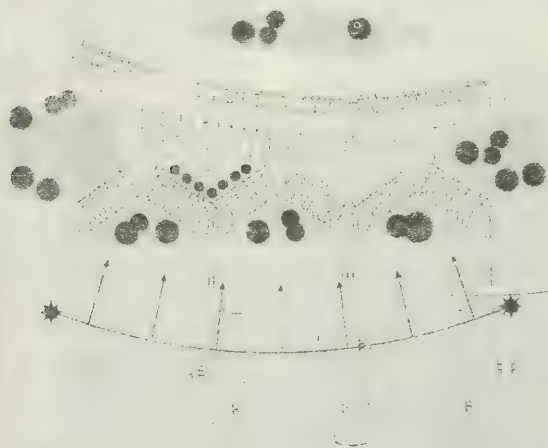


FLOOR PLAN VARIATIONS



ATRIUM

GARDEN ATRIUM



TYPICAL UPPER FLOOR PLAN

**KALLMANN MCKINNELL & WOOD
SKIDMORE, OWINGS & MERRILL**
Design Ranking: 2
Technical Ranking: 4 (tie)
Final Ranking: 2

After Kallmann, McKinnell & Wood (KM&W) was selected as a finalist, the Boston firm teamed up with SOM's New York office for its healthcare expertise. Although SOM is better known for its design than in healthcare work, Principal Michael McKinnell maintained that KM&W simply wished to team up with a firm equally strong in design and documentation.

This duality, however, is reflected in the team's submission. The gentle, moving patient-care volume to the north was fully integrated with the zigzagging lab block to the south. The labs reveal KM&W's rigorous planning, but the transitional space between patient rooms and labs drew criticism for creating a large, awkward zone.

Panel members appreciated the generous bay windows of the patient rooms fronting the wooded NIH grounds; the plan to incorporate landscaped courtyards inside; the building's moderate scale; and the brick frontpiece topped by an overhanging copper cornice. The concave figure of the building promises to draw in visitors rather than push them away. As McKinnell affirms, "This should be an accepting and caring building, not a monument." The NIH's Deputy Director of Intramural Research Michael Gottesman recalls that McKinnell recognized "there are few social needs higher than building a research hospital. He clearly understood what was essential."



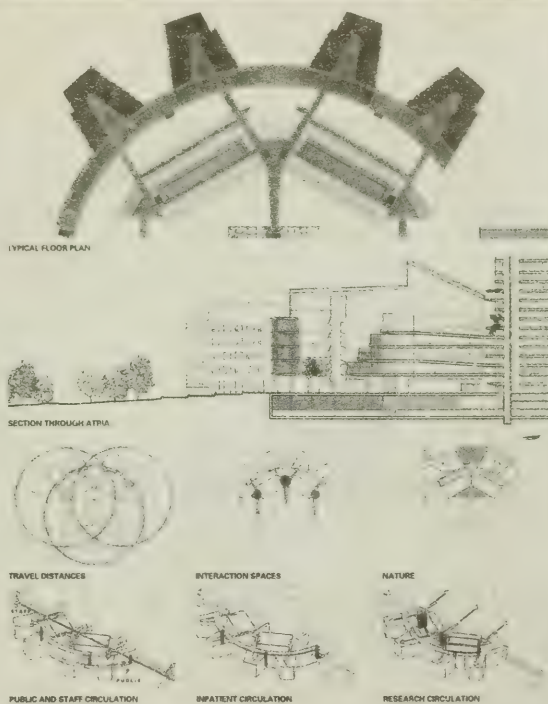
KOHN PEDERSEN FOX
HANSEN LIND MEYER
 Design Ranking: 3
 Technical Ranking: 4 (tie)
 Final Ranking: 3

The NIH competition represents Kohn Pedersen Fox's first foray into laboratories. As a result, the New York firm teamed up with Hansen Lind Meyer, a firm experienced in research facilities. Their scheme was in many ways the most radical of the six, inspiring the strongest reactions both for and against it.

A quartet of large radial patient-care units pushes forth assertively into the landscape from a curving spine that is connected on the south to two lab blocks, each rotated 30 degrees from Building 19's east-west axis. The strong, figural plan "leapt off the boards," recalls Project Manager Walter Armstrong.

The selection panel praised the natural elements—daylight, vegetation, and water—introduced to the complex, and appreciated the way Principal William Pedersen sketched his ideas during his presentation. But KPF's inexperience with labs and healthcare design was evident in the rigid geometries of patient-care modules and the impractical configuration of nursing stations.

Moreover, the panel was concerned that splitting up the facility into multiple bays would raise the cost of construction above that of a more unified complex. The scientists felt that housing the clinical facility in several such modules might isolate researchers from one another, contrary to the idea of creating a single scientific community within the new complex.



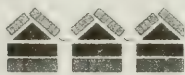


TYPICAL FLOOR PLAN



PLAN OF 12-BED PATIENT UNIT

■ PATIENT
 ■ NURSING
 ■ SUPPORT
 ■ RESEARCH



PUBLIC CONCOURSE

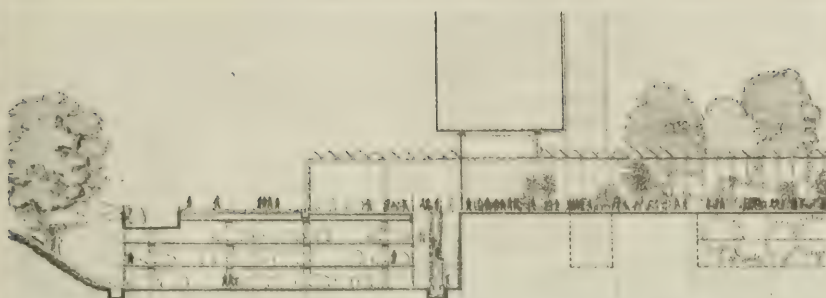
VENTURI, SCOTT BROWN AND ASSOCIATES
PAYETTE ASSOCIATES
 Design Ranking: 5
 Technical Ranking: 3
 Final Ranking: 4

Venturi, Scott Brown and Associates (VSB&A) and Payette Associates have long collaborated on laboratories, and their expertise was clearly evident in their efficient design for NIH. The selection panel discounted the building chiefly on esthetic grounds: its serrated brick facade, which looked more "repetitive than rhythmic," reminded several scientists of public housing projects.

Nonetheless, "It's the most workmanlike" of all the schemes, concludes Armstrong. "You could go out and build it tomorrow."

Extending from Building 10's north and south wings, the addition directly adjoins the ACRF's north side. Within the six floors, patient bays face north and labs face south. Every floor contains two 36-bed patient-care units, organized as six bays of 12-bed clusters, and each cluster backs up to a single laboratory module. Patient units and labs share common circulation spaces; the lab zone contains an additional support corridor.

The panel maintained that the design concept emphasizes corridors over spaces for social interaction, which were listed as a priority in the program. However, lounges inserted between the health-care bays with views of the campus provide respite areas for patients and their families.



RENZO PIANO BUILDING WORKSHOP

Design Ranking: 4

Technical Ranking: 6

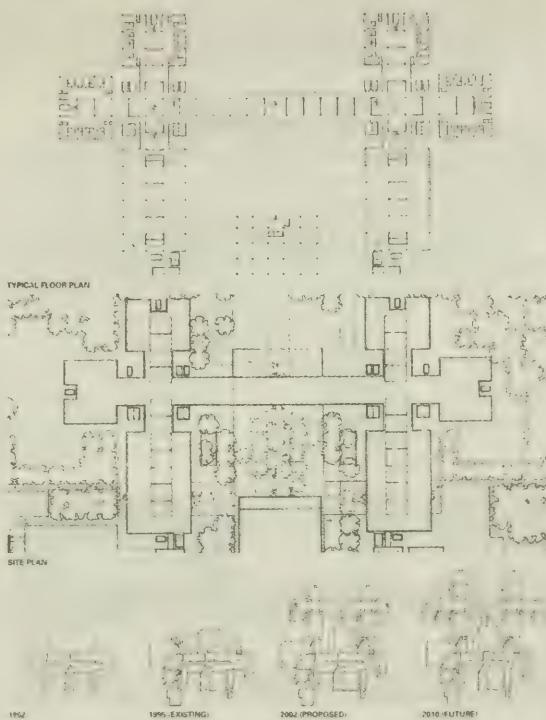
Final Ranking: 5

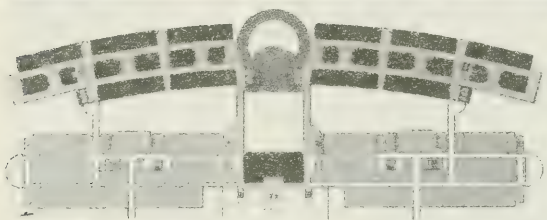
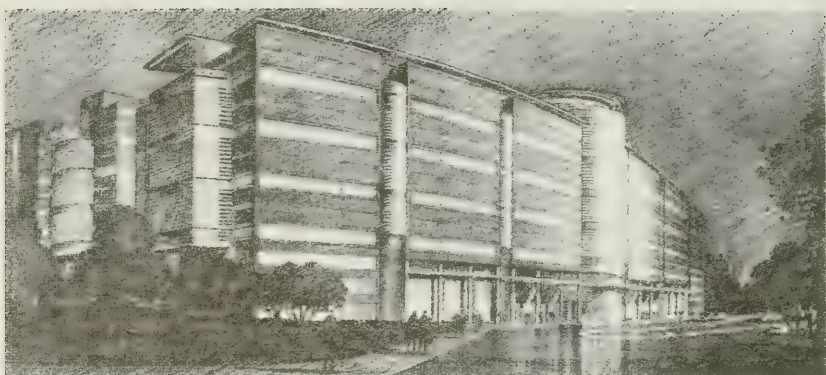
Renzo Piano unabashedly proposed a monumental 12-story companion to the existing Clinical Center. "We tried to replicate the DNA of Building 10," Piano explains, describing his plan to extend the 1952 building's east and west wings. The Italian architect designed his new complex to the same scale as Building 10, echoing the original building's massing with an H-shaped block of labs and patient-care rooms.

Patient units are paired around each north terminus, allowing four 18-bed units per floor. Unlike most of the competition's schemes, in which patient rooms face exclusively north, Piano's patient rooms are oriented in all directions, while lab blocks face east and west.

A central plaza extends under the new and existing buildings to underscore a new campus axis suggested by NIH's current master plan. Piano's proposal permits future expansion with plans to augment patient blocks with identical units located to the north, east, and west.

The large scale of Piano's proposal and his process approach to architecture, however, ultimately lost him support. Explains Gregory Curt, clinical director of the National Cancer Institute, "He imagined the grandeur of schemes, and his concept of looking at the campus as a 'small city' was right on." Although the panel responded enthusiastically to the poetics of Piano's proposal, the statisticians were not seduced by the monumentality of his idea.

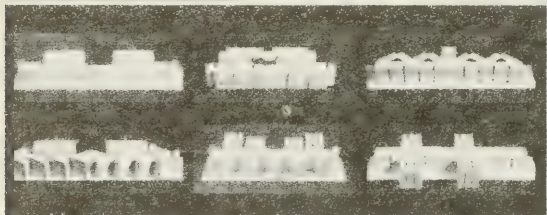




TYPICAL FLOOR PLAN



SECTION THROUGH TYPICAL PATIENT CARE AND LAB WINGS



PROPOSED ALTERNATIVE SCHEMES

CESAR PELLI & ASSOCIATES
HKS/LEO A DALY
 Design Ranking 6
 Technical Ranking 2
 Final Ranking: 6

The Pelli team's scheme suffered as much from its unconvincing presentation as from its large-scale parts. Pelli emphasized "process over image," and presented more siting and massing alternatives than competitors did. But the architect chose to focus on the least attractive of them: a monolith that struck the jury as the Great Wall of China—a barrier rather than a gateway to the campus.

The long, curved patient-care wing faces north and flanks a cylindrical circulation core. Across a courtyard to the south, the lab modules and support spaces are housed in a separate block abutting the A/R/E, which connects to the patient-care units via glazed bridges. Labs and patient-care areas are placed at levels 4, 6, 8, and 10 between interstitial floors, to align with existing floors within the A/R/E block. A large interior public court between patient and lab wings extends a north-south axis to an auditorium on Building 10's south side.

Pelli like his building to be a "tough machine" of great efficiency. To humanize its face, the architect presented examples of the variegated brick detailing typical of his recent projects, but even such meticulous craftsmanship was unlikely to soften the edifice's scale, which the jury deemed too monumental.

COST ESTIMATE FOR CRC

Mr. PORTER. All right. Why don't you do that for each member of the subcommittee, because I think they'd like to see it.

How can you have a very accurate cost estimate for a hospital until the detailed architectural plans are developed?

Dr. VARMUS. Well, that's an extremely good question. Of course, we don't have a very accurate number—we provide an estimate. We think we can work within that estimate. We're only going to have a precise accounting after more detailed planning, but—we're going to work within the figure that is appropriated. We cannot tell until we have a very detailed design what the precise costs would be.

CRC PROJECT MANAGEMENT

Mr. PORTER. We understand that you have contracted with a project management firm, rather than use NIH employees to supervise construction of the hospital. Is this a common practice in the Federal Government, and why do you think it is needed for the clinical center?

Dr. VARMUS. It is an increasingly common practice, Mr. Porter. It's been used by a number of agencies. It promotes efficiencies, and it allows one firm to be accountable for all the activities of the construction project. The managers, in this case Boston Properties, will be awarding all the contracts that are responsible for all phases of the construction.

We think there will be extensive savings. Agencies that have used it have been very pleased with the efficiencies that are generated. I believe that by being able to point to a single firm, which is accountable for all these activities, we will have a tremendous degree of security in proceeding with the project.

INFRASTRUCTURE MODERNIZATION

Mr. PORTER. Now a question unrelated to the, or at least not directly related to the proposed new clinical center. Your budget includes a substantial amount for infrastructure modernization, \$43 million, and repairs and improvements, \$26 million. Is this the result of long periods of budgetary neglect? And should we handle budgeting for this activity differently? For example, setting aside a fixed contribution each year tied to the effective life of a building?

Dr. VARMUS. Well, the first part of your question I believe is really answerable by looking at what we are going to be doing with that increase in the infrastructure modernization program this year. That is, we're going to have to address the chilling and heating units that serve the existing Building 10. That's a project which needs to be undertaken in the course of a single year or two, with a single appropriation.

Mr. FICCA might want to comment further about the nature of that project.

Mr. FICCA. Well, the infrastructure modernization program has been ongoing for about seven years. It's a nine year program in total. And to answer the first part of your question, yes, partially, it is due to insufficient maintenance and repair funding over the

years. The project, because of budget constraints, has been phased out longer that it probably should have.

And at this point in time, the amount of money that we're requesting is for a crucial expansion of the power plant to install a new chiller that will address the insufficient heating and chilling capacity required over the next three years.

Dr. VARMUS. As for the other part of your question, Mr. Porter, I don't have a firm answer at this point. But I think it raises an interesting question about whether some means to protect against the inevitable decline of our buildings should be built into our budget.

Mr. PORTER. Thank you, Dr. Varmus, and thank you, Mr. Ficca.

I have been called to the Floor to address our section of the Omnibus Appropriations Bill. I'm going to ask Mr. Istook to take the chair and Mr. Istook will finish this portion of our afternoon hearings, and then proceed into the Office of the Director.

Mr. Istook.

HISTORICAL CONTEXT OF PROJECTS

Mr. ISTOOK [assuming chair]. Dr. Varmus, continuing on the building part, obviously since it's the main request, and we are devoting much more time to it than to the Director's Office, I would be interested, of course, and I know you can help us compile kind of a lookback on historically for the last, I don't know what's the best significant number of years, five years, ten years, whatever it may be, of the construction projects and the improvement projects, to put these things in that historical context.

And we can get that from you, but I would like to ask you at this time, take us forward to beyond fiscal year 1997. Give us some perspective of how these things are intended to fit into the plans for the next, say, five years. And of course, this could be supplemented in writing, it would be helpful, too.

Dr. VARMUS. You're asking: Are there other construction projects that are on the drawing board?

Mr. ISTOOK. Sure. I want to fit this into not only the historical time frame, but the projected future expansions or improvements that you desire.

Dr. VARMUS. This is the last major project that we can foresee for at least the next 10 years or so. There would be an option, as I described earlier, of setting up a renovation program for the remaining space in the existing Building 10, the Clinical Center complex.

There is the prospect of renovating the space that would be vacated by moving the hospital and the 11 percent of laboratory space we alluded to before. Because of the freed-up swing space, there is also the possibility of renovating other parts of the building, these are also inadequate from many points of view. They are functional at the moment, and no patients are housed in them. But they represent sub-standard laboratory space for the current era.

Mr. ISTOOK. So if you were trying to give some, and I realize it might be rough, but at least some financial projection of whether it would be that renovation project or whatever you, I forget the term you used, of more usual or normal numbers, I don't know what you would consider the plateau of what normal is. You can

look, I think the current year is \$146 million, the year before \$114 million. I'm not quite sure what that means in trying to anticipate what future possibilities might be, both for what you might call a basic maintenance level as well as for potential renovations.

Dr. VARMUS. Well, we are going to have maintenance and repair ongoing. We have a large number of buildings on the campus and any institution as you know, the University of Oklahoma or any other institution needs to maintain and repair its buildings as time goes on. And we would anticipate that something on the order of \$50 million to \$100 million a year, I'm not sure that's a fair number, something of that magnitude, would be required simply to keep our buildings at adequate repair.

Mr. ISTOOK. Okay. And obviously, if you can supplement that in a little bit more detail, a little bit more precision than \$50 million to \$100 million range, that would help.

Dr. VARMUS. Certainly, yes.

[The information follows:]

MAINTENANCE AND REPAIR

The NIH computes its annual cost of maintenance and repair using the National Academy of Sciences (NAS) 1990 Report "Committing to the Cost of Ownership". The report states that typically the maintenance and repair levels depend on the intensity of the use of the space and will be 2 to 4 percent of the current replacement cost of the facilities. This cost represents the minimum investment needed to maintain the facilities in their current condition. For 1997, using the NAS algorithm, the NIH projects a maintenance and repair cost level of \$124.5 million. This is based on the total floor area of NIH facilities of 11.0 million square feet and a replacement value of approximately \$3.5 billion. Using the NAS guidelines, the minimum investment for the NIH to maintain its facilities in their current condition by FY 2002 would be approximately \$173,000,000 and then approximately \$212,000,000 by FY 2007, at the ten year interval.

REVIEW OF COMPARABLE PROJECTS

Mr. ISTOOK. Especially because, you know, if this project is to go forward, the subcommittee, of course, has to look at options of multi-year funding with an actual outlay stream.

Dr. VARMUS. I understand that.

Mr. ISTOOK. And to understand those.

I also wanted to ask, Dr. Varmus, you said that you looked at 17 other projects to try to get a rule of thumb regarding anticipated square footage costs. Is 17 basically the full universe of comparable projects within the last five years or whatever, or it's just those that you thought were most comparable institutions?

Dr. VARMUS. We took institutions that were largely in areas where the building costs were likely to be similar to the costs that would be incurred in this area. We also used research-intensive institutions, so we would not have compared it with a rural community hospital, for example, where I don't think the cost comparison would be appropriate.

Mr. ISTOOK. And I realize, you know, it's not feasible for anything to think of taking an institution that's got an established campus, and with the construction that's been there, such as NIH, and saying, well, let's go someplace in the country where the cost of living is lower. But it would be useful to us, nevertheless, to have the comparisons of other projects, even if they were not in areas where the cost of living was comparable. If you could provide

us with that information, not just the subset that relates to those of——

Dr. VARMUS. You're asking for published numbers. You're not asking us to undertake a study?

Mr. ISTOOK. No, I'm not asking for a study. I realize you're using some resource to get those numbers from, and I'm not asking for an elaborate study. But I would like to have that information on these facilities that were located elsewhere.

Dr. VARMUS. We'd be happy to do that. We could look at some academic health centers in some of the rural states.

[The information follows:]

SURVEY OF ACADEMIC HEALTH CENTERS

The following facilities provided a basis to establish construction unit costs for the Clinical Research Center (CRC). The estimated unit costs for the CRC are also included for comparison. These unit costs include only actual construction costs and do not include design fees, management fees, contingencies, major site and utility work, and land acquisition:

Hospitals	Locations	Unit Costs (1996)	Unit Costs (2000)
NIH Clinical Research Center 1/	Bethesda, MD	\$250/SF	\$285/SF
Boston City General Hospital	Boston, MA	\$262/SF	\$299/SF
Bronx Lebanon Hospital	New York, NY	\$305/SF	\$347/SF
Madigan Army Hospital	Seattle, WA	\$225/SF	\$257/SF
University of Virginia	Charlotte, VA	\$227/SF	\$258/SF
University of Michigan	Ann Arbor, MI	\$224/SF	\$256/SF
V.A. Hospital - Baltimore	Baltimore, MD	\$163/SF	\$185/SF
V.A. Hospital - Philadelphia	Philadelphia, PA	\$179/SF	\$204/SF
St. Mary's Hospital	Waterbury, CT	\$307/SF	\$350/SF
Norwalk Hospital	Norwalk, CT	\$282/SF	\$321/SF
Albany Medical Center	Albany, NY	\$256/SF	\$292/SF
St. Vincent's Hospital	Staten Island, NY	\$263/SF	\$305/SF
St. Catherine's Hospital	Chicago, IL	\$221/SF	\$253/SF
Bradford Hospital	Bradford, PA	\$236/SF	\$269/SF
John Dempsey Hospital	Farmington, CT	\$275/SF	\$314/SF

Laboratories	Locations	Unit Costs (1996)	Unit Costs (2000)
Boston University	Boston, MA	\$294/SF	\$336/SF
Genetic Research Lab	Cambridge, MA	\$314/SF	\$358/SF
UCLA	Los Angeles, CA	\$312/SF	\$356/SF
Rutgers University	Trenton, NJ	\$330/SF	\$370/SF
University of Pennsylvania	Philadelphia, PA	\$300/SF	\$342/SF
Case Western University	Cleveland, OH	\$242/SF	\$277/SF
Center for Disease Control	Morgantown, WV	\$262/SF	\$299/SF
University Biomedical Lab.	New York, NY	\$372/SF	\$425/SF

The above construction unit costs were escalated to constant 1996 dollars for purposes for providing a uniform comparison. These unit costs, escalated to the year 2000, represent the estimated unit costs of construction (estimated to mid-point of construction) at time of bid opening for the Clinical Research Center project.

1/ The cost of \$250/SF is only for construction of the Clinical Research Center. The actual cost of the facility including design and construction is estimated to be \$370/SF.

PATIENT LOAD BY DISEASE

Mr. ISTOOK. Certainly. And that way, we'd kind of have a look at the full constructions of facilities, as well as those in different costs.

On the patient load of the existing center, do you adjust as you track by institute in different disease, sort of like we covered before, spending on basis of different disease, do you track in the clinical center the patient load and patient days basically by disease as well?

Dr. VARMUS. We could provide that information.
[The information follows:]

The Clinical Center monitors by protocol activity and has a review of patient accrual to each protocol twice yearly with each Institute Clinical Director and Scientific Director. Based on these reviews, ICDS make adjustments as appropriate.

Dr. VARMUS. You will find, of course, Mr. Istook, that the proportionality would not necessarily be in accord with the financial impact of the disease. Because one of the virtues of the clinical center, is to act as a central resource for rare diseases that are of extreme medical interest, and for which there is not an adequate patient population any single place around the country. That's one of the advantages of being a magnet institution.

Mr. ISTOOK. Sure. Right, and especially because, as you mentioned, you're certainly going to have some rare diseases that are going to be treated there, too.

Dr. VARMUS. Right.

Mr. ISTOOK. But I think it would be useful, not only of a one year snapshot, and I don't know what's the easiest and appropriate period of years, whether doing eight years is just as easy as doing four or five years.

Dr. VARMUS. It probably is. We presumably have diagnoses for all the patients and we could provide that information very easily.

Mr. ISTOOK. Sure. That historical context will be helpful.

I think I probably have some other questions I might submit for the record on that.

[The information follows:]

CLINICAL CENTER TOP TWENTY DIAGNOSES BY FISCAL YEAR: INPATIENT

FISCAL YEARS 1995 - 1991
TOTAL DISCHARGES - 42,506

Diagnosis	COUNT*					
	5 Year Total	FY95	FY94	FY93	FY92	FY91
Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome	1323	290	314	257	233	229
Essential Hypertension, unspecified if benign or malignant	1207	211	218	254	271	253
Melanoma of Skin, site unspecified	1108	172	247	226	222	241
Secondary Malignant Neoplasm of Lung	1093	162	173	242	238	278
Malignant Neoplasm of Female Breast	1083	160	168	298	273	184
Malignant Neoplasm of Ovary	981	151	181	235	225	189
Unspecified Hypothyroidism	924	128	168	204	227	197
Malignant Neoplasm of Kidney, except pelvis	917	175	158	166	200	218
Secondary Malignant Neoplasm of other specified sites	786	114	147	157	159	209
Secondary Malignant Neoplasm of Liver	782	107	128	172	192	183
Pyrexia of unknown origin	769	104	122	179	176	188
Chronic Ischemic Heart Disease, unspecified	728	126	143	144	159	156
Cushing's Syndrome	720	0	142	182	191	205
Lack of Expected Normal Physiological Development	591	0	133	141	174	143
Wegener's Granulomatosis	544	0	0	170	194	180
Agranulocytosis	540	0	0	158	197	185
Diabetes Mellitus, without mention of complication-Type II	529	97	122	0	157	153
Pure Hypercholesterolemia	471	101	109	119	142	0
Abnormality of Secretion of Gastrin	464	110	105	109	140	0
Other Lymphomas, unspecified site	410	148	120	142	0	0
Endomyocardial Fibrosis	408	97	0	0	154	157
Depressive Disorder, not elsewhere classified	235	111	124	0	0	0
Secondary Malignant Neoplasm of Bone and Bone Marrow	170	0	0	176	0	0
Systemic Lupus Erythematosus	161	0	0	0	0	161
Viral Hepatitis B without mention of hepatic coma	152	0	0	0	0	152
Malignant Neoplasm of Prostate	111	0	111	0	0	0
Function Disorders of Polymorphonuclear Neutrophils	105	105	0	0	0	0
Other Primary Cardiomyopathies	95	95	0	0	0	0

* Total discharge diagnoses from the NIH Warren G. Magnuson Clinical Center; a patient discharged x times from the Clinical Center will receive a count of x.

Mr. ISTOOK. I think that would be all I wanted to explore at this time on that. So I appreciate that, and I guess we ought to move to Dr. Kirschstein and the Director's Office, unless there is anything else that you or anyone with you wanted to add on the buildings and facilities.

[The following questions were submitted to be answered for the record:]

CLINICAL RESEARCH CENTER RENEWAL

Mr. Porter: What is the present usable square footage of the Clinical Center Complex, and what will it be after construction of the new hospital and renovation of the existing space?

Dr. Varmus: The current usable square footage of the Clinical Center Complex is approximately 1,237,000 square feet (not including the parking garage). With the completion of the new Clinical Research Center and the renovation of the existing building, it is anticipated that the existing Clinical Center Complex will have between 800,000 and 900,000 usable square footage. This reduction of usable square footage is necessary to provide adequate space for the distribution of utilities to provide a modern and flexible facility.

The 12 feet floor to floor heights and the interior concrete support beams severely limit the space for the distribution of utility systems. Building interstitial space within the existing Building 10 is extremely difficult. It is anticipated that partial interstitial space will be used in the renovation of the existing facility to provide the flexibility to support a modern laboratory facility thereby reducing the usable square footage within the renovated structure. While further studies are planned, at this juncture this approach appears to be the most cost effective in terms of renovations and operating costs.

Mr. Porter: How many additional years of useful life will the existing Clinical Center have after the essential maintenance and safety repairs are complete?

Dr. Varmus: The Essential Maintenance and Safety (EMS) Program will extend the useful life of the existing Clinical Center approximately 12 to 15 years. The EMS program was intended to be a stop gap measure to extend the useful life of the Clinical Center by replacing/rebuilding the dynamic systems, fans, pumps, etc., that are now at or very near the end of their useful life. These are central units and can be replaced while the facility is occupied. The static distribution systems in the original Clinical Center, such as ductwork and piping, currently have an expected remaining useful life of about 12 years. These static systems, primarily located in occupied space, cannot be effectively upgraded without vacating large blocks of contiguous space. This so-called swing space will be provided by occupancy of the new Clinical Research Center in about five years. The EMS addresses the immediate problem of insufficient ventilation and extends the useful life of the facility 12 to 15 years until a more comprehensive plan can be implemented to replace the static systems within the occupied space. The new equipment being installed under the EMS will be reused with the future renovation sequence.

MASTER PLAN

Mr. Porter: Summarize the guiding principles of the NIH campus master plan in terms of the size of the campus, the consolidation of off-site facilities, and the number of additional buildings slated for future construction.

Dr. Varmus: The master plan has not been approved by the Department or OMB. It is important to emphasize that it is not a budget document or even a construction plan. The master plan is merely a road map to guide us in terms of future facilities needs. The extent any of the elements of the Plan are implemented depends upon future resource and budget availability, as well as evolving needs and policies.

The 1995 NIH master plan accommodates a campus employee population growth over a 20-year time frame from about 16,000 currently to a maximum of about 18,000 personnel in the year 2015. The primary growth at the campus would be through potential consolidation of intramural research program personnel from other NIH sites to the Bethesda campus. Providing space for these personnel estimates, including decompression of currently overcrowded office and laboratory space, accommodation of utility upgrades, and addition of needed amenities, the master plan proposes a net growth of space on the Bethesda campus from approximately 7 million to 10 million gross square feet. Much of the building area growth will be accommodated through the redevelopment of the campus core in a more efficient manner. Most of this growth is in replacement and modernization of intramural research laboratories and the proposed 850,000 square foot Clinical Research Center. Other specific projects in the master plan include a consolidated laboratory building, a replacement animal facility, replacement facilities for some service and support functions, and the construction of up to 11 new or replacement laboratory buildings.

MEDICAL WASTE DISPOSAL

Mr. Porter: Does NIH meet current medical waste disposal requirements, especially for radioactive waste?

Dr. Varmus: The NIH has an established process for the collection and disposal of medical waste. A unique packaging system which provides for the protection of workers who collect and process the waste for ultimate disposal is utilized. Medical waste is packaged at the site of generation, collected from each building on a daily schedule, transported to a central on-campus site to be screened for possible radioactive materials and then transported by a licensed contractor to a remote licensed medical waste incinerator. Cartons identified as containing radioactivity are segregated out of the waste stream for additional assessment to determine the radioactive material present in the waste. If the radionuclide has a half-life of less than 100 days, the waste is held until the radioactivity decays to a level where the waste can be reclassified as non-radioactive and is suitable for routine disposal. Waste containing a radionuclide having a half-life of greater than 100 days is disposed of in accordance with the procedures established by the Nuclear Regulatory Commission and the Environmental Protection Agency for the disposal of low-level, solid radioactive waste.

CLINICAL RESEARCH CENTER RENEWAL

Mr. Porter: When in 1996 do you expect to issue the contract for the architectural design for the Clinical Center?

Dr. Varmus: It is expected that the design contract could be awarded to the Zimmer Gunsul Frasca (ZGF) Partnership by June 1996.

NIEHS ADDITION

Mr. Porter: Your 1997 budget does not request further funding for the construction project at NIEHS. Does the funding provided in the 1996 appropriations bill represent the last payments for this building?

Dr. Varmus: The \$6 million provided in the FY 1996 appropriation represents the last payment for the NIEHS Laboratory Addition, as well as changes/additions to the Central Utility Plant necessary to support the facility.

CLINICAL RESEARCH CENTER RENEWAL

Mr. Porter: Explain the present budgeting mechanism for the Clinical Center and how the costs of operating the center are allocated among the Institutes.

Dr. Varmus: The Clinical Center's budget is developed annually to support the intramural clinical research mission. The operating level is set by the Central Services Review Committee, as are all other components of the fund. The Clinical Center is funded through the NIH Management Fund, a mechanism by which each Institute pays for a portion of services provided based on an allocation formula. The allocation formula divides the costs of operating the Clinical Center to each Institute based on a retrospective and a prospective component. The retrospective component, comprised of fixed costs which represent 80% of the Clinical Center budget, is based on historical use by an Institute over a three-year period. Variable costs, the remaining 20% of the budget comprised of prospective and retrospective elements, are allocated based on Institute plans. Each Institute presents a plan for clinical care use related to the variable prospective costs and the Clinical Center estimates the costs of the proposal based on the number and acuity of inpatients and outpatients proposed.

The current budget process is under revision at the recommendation of the REGO II Options Team, chartered by Secretary Shalala, to identify ways to improve the operations of the Clinical Center. The Options Team concluded that the Clinical Center budget mechanism is complicated, provides no incentive for either the Clinical Center or the Institutes to increase efficiency, is far more unstable than funding of NIH as a whole, and provides no way to encourage increased use of the Clinical Center so as to lower unit costs.

The Options Team recommended that the Clinical Center should have a clearly defined budget of its own which should be no less inherently predictable than the

budget of NIH as a whole; allow savings to be retained and reinvested within the Clinical Center from year to year; ensure that all Institutes have continued access to a baseline level of activity; permit Institutes that sharpen their forecasting; that the Clinical Center change insurance companies for some services; and improve the efficiency of their program to increase overall activity. The President's FY 1997 budget follows up on the Option Team's recommendations by requesting authority for NIH to collect \$18 million in third party payments for services provided in the Clinical Center and requesting that funds for the Clinical Center be made available for two fiscal years. The Clinical Center is developing a new funding mechanism which meets these criteria.

Mr. Porter: Do you expect the Vice President to declare the Clinical Center a reinvention laboratory?

Dr. Varmus: No, such a formal declaration of "reinvention laboratory" status is not needed to accomplish most of the recommendations of the REGO II Options Team. To help meet the objective of ensuring more stable funding for the Clinical Center, the FY 1997 budget requests appropriation language to allow funding from the NIH Management Fund, which supports the Clinical Center, available for two fiscal years. The NIH budget request also proposes language to allow NIH to collect and retain third party reimbursements for some patient services provided at the Clinical Center, as recommended by the Options Team.

Mr. Porter: How can the Clinical Center increase its interaction with the extramural community?

Dr. Varmus: Intramural/extramural collaboration and cooperation have been increasing steadily over the past decade. Many ICDs have developed creative and innovative mechanisms to facilitate collaboration. These collaborative efforts can be categorized into several different types of activities, including utilization of expensive, rare technologies; access to unique cohorts of patients; access to clinical and scientific expertise; access to mentors/laboratories for post-graduate training and sabbaticals; collaborative research projects; and training opportunities in clinical research.

The Clinical Center is also entering into intellectual partnerships with several outside institutions, including the Johns Hopkins University Hospitals, the Georgetown University Hospitals and Clinics, the Howard University Hospital, the National Rehabilitation Hospital, Maryland's Suburban Hospital, and other community hospitals. Several Clinical Center and NIH investigators collaborate in numerous multicenter studies and on individual projects with external investigators who share mutual interests and expertise. As these pilot programs begin to bear fruit, we envision creating more such partnerships.

The Clinical Center has also initiated a program to make available to the extramural community the scarce resources (e.g., positron emission tomography) unique to the Clinical Center. The new Clinical Research Center will have capacity available for use by extramural investigators (approximately 25 clinical research

beds). Clinical Center and NIH administration are evaluating mechanisms to make this capacity available, on a competitive basis, to all extramural investigators who have an interest in conducting clinical research using the unique infrastructural resources of the Clinical Center.

As the Clinical Center's primary mission is the conduct of translational research, the scientists working at the Clinical Center necessarily must form ties with individuals working in the extramural community to assure that the findings of the phase I and II trials conducted at the Clinical Center can be translated into the practice of clinical medicine in the community. The future for these interactions is bright and should be facilitated by technological advances, such as telemedicine, which will be used in the new Clinical Research Center to link Clinical Center investigators with clinicians, scientists, and patients from around the country who are involved in Clinical Center research projects.

Mr. Porter: Do visiting professors and local clinicians have the opportunity to use the Clinical Center's facilities?

Dr. Varmus: As noted above, intramural/extramural collaboration and cooperation have been increasing steadily. Over the past year, a program has been initiated to allow the scarce resources unique to the Clinical Center to be made available to the extramural community (e.g., positron emission tomography resources were made available to a professor at the Rockefeller University). Additionally, several local clinicians serve as consultants in a variety of clinical specialties and subspecialties, including cardiology, gastroenterology and orthopedics, among others. Some of these consultants also participate as associate investigators on certain clinical research protocols. During the past few years several ICDs have had visiting professors and academic investigators here on sabbaticals. One ICD developed a concept called a "clinician sabbatical year" in one of their clinical branches. The first recipient of this award spends one to two days a week in the Clinical Center and the remainder at his home university in Philadelphia. Another ICD has developed a program that incorporates senior extramural investigators as collaborators for three months to one year in the intramural research program (often in the Clinical Center) through an IPA mechanism. NIH has also developed collaborative relationships with the local academic medical community. For example, one ICD intramural program has funded a large, longitudinal study in an adjacent major metropolitan area. As a result of this study, close collaboration has developed among intramural ICD staff and the staff of a major medical school in the same city. Additionally, intramural ICD scientists function as full collaborators with a senior investigator at George Washington University Hospital who also functions as an NIH guest worker. His protocols align with the ICD mission and are therefore funded by the ICD's intramural program. A former fellow from a third ICD has maintained a collaborative relationship with the laboratory in which she worked when she was at NIH. One of the projects on which she worked has been continued at both the Clinical Center and in her new institution (with IRB approval at both institutions).

Mr. Porter: What are the plans for integrating and upgrading the Clinical

Center's data systems for clinical management information? What is the estimated FY 97 and total costs of this project?

Dr. Varmus: The Clinical Center Medical Information System (CCMIS) is an advanced computer based information system used to support patient care and clinical research at the Warren G. Magnuson Clinical Center. It consists of multiple components and is designed to be used directly by doctors, nurses, and other health care providers. This architecture allows the Clinical Center to replace components regularly as it becomes technically feasible.

Over the past two years, the Clinical Center has developed and installed the technology to move the existing system to a totally network based architecture. Over the next several months, the remaining user workstations will be moved onto the network for a total of over 800 network based workstations with integrate to the CCMIS. With network access, doctors and nurses will be able to access new tools for patient care and clinical research easily and inexpensively. Such tools include Grateful Med, a wide variety of World Wide Web medical applications and data bases, as well as local applications for analysis and presentation of clinical and research data. In addition, access over the network has been enhanced to include data encryption and a secure and reliable form of user authentication so access can be extended to patient care staff from outside the Clinical Center. This will bring multiple benefits of productivity, flexibility, and potential collaborative work with non-NIH staff while ensuring patient confidentiality. A comprehensive and standardized set of applications needed to support patient care and clinical research will be installed on each workstation. This project is called the "standard clinical desktop environment" and is well along toward completion.

The existing separate laboratory computer systems serving the Departments of Clinical Pathology, Transfusion Medicine, and Anatomic Pathology will be replaced by a single more comprehensive system meeting the needs of all three departments, as well as a more integrated database for patient care and clinical research.

The Clinical Information Utility, a very large database of 500 million clinical observations extending from 1975 to the present, is being converted to a network based "clinical data repository" to facilitate access by clinical investigators and patient care staff at the NIH. The existing system is batch oriented and does not allow ease of access or integration with other systems.

In conjunction with this project, efforts are in place to install an "interface engine," which is a specialized medical information translation computer that translates data from the format of one computer to that of others that need the information. This will allow us to easily and immediately send data among the various components of the CCMIS and to specialized clinical research systems that are part of specific Institute databases. Research systems from NCI and NIAID are examples that will be connected to the interface engine.

Hospital management data is currently obtained as extracts from the clinical

databases and combined with data from central NIH fiscal and management systems. The Clinical Center is evaluating the costs and benefits of shifting to a more hospital-oriented management system for data collection or whether instead to acquire a specific hospital executive information data analysis system that would provide data by enhancing the extractions from the current system supplemented by data from NIH-wide central systems.

Video conferencing and telemedicine are projects underway which are targeted for expansion in FY 1997. The Clinical Center (in conjunction with the National Institute of Allergy and Infectious Diseases) is working with Texas physicians to build a collaboration to jointly study patients with multiple drug resistant tuberculosis. Several clinic rooms in the Clinical Center Ambulatory Care Research Facility (outpatient tower) will be designated as video conferencing sites. Use of video conferencing and telemedicine technologies will help the Clinical Center to achieve the following goals: a nationwide, collaborative approach to conducting clinical research; access to patients throughout the country for screening for participation in research studies; reduced travel costs associated with clinical research; and improvement in follow-up and continuity of care by allowing NIH physicians and scientists to interact directly with patients and physicians at remote sites.

The FY 1997 budget estimate for computer systems activities is \$7 million.

CLINICAL RESEARCH CENTER RENEWAL

Mr. Porter: If funds were provided according to the timing of when obligations will occur, what would be the stream of funding for the Clinical Center?

Dr. Varmus: In order to effectively carry out the Clinical Research Center construction project of a total of \$310 million to be phased over four years, we would need \$90 million for each of the first three years and \$40 million in the last year.

Mr. Porter: You are planning a 250-bed hospital, down from the current total of about 325 beds being used. Aside from the Marks-Cassell intramural review, were there any other independent projections made of the appropriate bed size of the facility?

Dr. Varmus: No, however, in planning for the new Clinical Research Center, a steering committee comprised of engineers, architects, and primarily internal administrators interviewed members of the intramural research community as to problems with the current facility and future programmatic needs. In discussing the size of the new facility, the committee considered that the Clinical Center is a clinical research facility which has specialized requirements which differ from primary care hospitals. For example, the size of the Clinical Center must accommodate the requirement that patient volunteers be available when needed for the research protocols. Since many patients are discharged on the weekends, the bed capacity must be, at a minimum, large enough to meet the peak week day requirement of 200 beds. Additionally, as with any other hospital serving acutely ill patients, capacity must be

available for emergency admissions.

The committee determined that a 250-bed Clinical Research Center is the appropriate size to support the current activity level based on the following programmatic considerations:

- 1) Relocation of off-site clinical research programs to the Clinical Center, which will increase the average daily inpatient census by approximately 25 patients.
- 2) As a consequence of the shrinking availability of clinical research beds in university-based medical centers, clinical researchers at extramural institutions are already having (and are projected to have even more) difficulty finding resources for their studies. To provide access for extramural investigators to Clinical Center scarce resources, the Clinical Center has proposed opening its facilities to some extramural investigators, for which an additional 25-bed capacity is needed.
- 3) Programmatic expansions have been planned by several Institutes, but activity in these new programs has been somewhat limited by difficulty recruiting new patients. To alleviate this problem, the Clinical Center has established a patient recruitment center.
- 4) Financial constraints have reduced Institute use of the Clinical Center. To reverse this trend, a new funding structure is being established to provide an independent, stable budget for the Clinical Center, ensure ICDs a continued level of access to Clinical Center services and permit ICDs that sharpen forecasting abilities and improve operating efficiency to increase their activities.

Mr. Porter: What are the current occupancy rates for the hospital and what do you project for the new facility? Are you confident of these estimates even though occupancy rates at the Clinical Center have been on the decline for the past two decades?

Dr. Varmus: The Warren G. Magnuson Clinical Center opened in 1953 as a 500-bed hospital. In 1975, the Clinical Center maintained 460 beds to accommodate patient volunteers for more than 1,000 research protocols. At that time, the average daily census was more than 300 and the average length of stay was about 25 days. The Clinical Center bed capacity has been reduced in the last two years to about 325 beds, which is the smallest capacity possible to maintain program requirements within the current hospital configuration. Today, the Clinical Center supports 1,100 active research protocols, representing a stable level of overall research activity. The peak weekly non-holiday census has decreased to about 200 and the average length of stay has declined to 9 days.

The Clinical Center is a clinical research facility which has specialized requirements which differ from primary care hospitals. For example, the size of the Clinical Center must accommodate the requirement that patient volunteers be available when needed for the research protocols. Since many patients are discharged on the weekends, the bed capacity must be, at a minimum, large enough to meet the peak week day requirement of 250 beds. Additionally, as with any other hospital serving acutely ill patients, capacity must be available for emergency admissions.

Taking into account this peak week day requirement (likely to be fueled by the new budget process and the patient recruitment center, the assimilation of off-site programs, which requires 25 inpatient beds and a unit for extramural investigators to conduct clinical research, the new Clinical Research Center is expected to function at full capacity.

Mr. Porter: What excess capacity is built into the Clinical Center hospital design?

Dr. Varmus: With regard to space, there will be no excess capacity built into the new Clinical Research Center (CRC) design. The CRC will be the minimum size to meet the clinical and research mission requirements. The hospital component will be sized to accommodate the identified clinical needs of the Intramural Research Program, plus consolidation of inpatient programs currently conducted off campus by two Institutes, plus a small allowance for provision of facilities to extramural clinical investigations. The laboratory component will both accommodate the clinical labs that require immediate adjacency to the patient care areas and facilitate the likely future phased renovation of the original Building 10. The Clinical Research Center architectural and systems design will provide for the future and efficient conversion of blocks of space from laboratory to patient care, or vice versa, should the need arise.

The systems capacity built into the new Clinical Research Center will not exceed the basic identified and programmed requirements. The flexibility and adaptability of these systems, so as to be responsive to changes in research needs, is a primary consideration and will be stressed in the design process. This major factor and the need to quickly and efficiently alter occupied areas will be facilitated by interstitial systems spaces.

Mr. Porter: What assumptions have you made about the percentage of care to be provided on an in-patient versus out-patient basis? How does that compare to current Clinical Center experience?

Dr. Varmus: Although the volume of services required to support an inpatient day exceeds that of an outpatient visit, the number of inpatient days and outpatient visits have been roughly equal since FY 1991. It is anticipated that this relationship will continue with the opening of the new Clinical Research Center. Should this trend change, the new facility will have areas which can be easily converted from inpatient to day hospital capability and vice versa. This feature will enable CRC management to meet the changing needs of the Institute research programs in an economical and efficient manner.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

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NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

For the study of, construction of, and acquisition of equipment for, facilities of or used by the National Institutes of Health, including the acquisition of real property, \$420,000,000, to remain available until expended.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation ^{1/}

	<u>1995</u> <u>Actual</u>	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>
Appropriation	\$114,120,000	\$146,151,000	\$420,000,000
Unobligated Balance, start of year	245,073,000	141,510,000	—
Unobligated Balance, end of year	<u>-141,510,000</u>	<u>—</u>	<u>—</u>
Total obligations	217,683,000	287,661,000	420,000,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1995 — \$5,100,000, FY 1996 — \$3,181,000.

JustificationBuildings and Facilities

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Total budget authority	\$114,120,000	\$146,151,000	\$420,000,000	+\$273,849,000
Total obligations	(217,683,000)	(287,661,000)	(420,000,000)	(+132,339,000)

General Statement

The Buildings and Facilities appropriation provides for the design, construction, improvement, and major repair of clinical and laboratory buildings and supporting facilities essential to the biomedical research mission of the National Institutes of Health. Funds are provided for non-recurring direct construction projects as well as ongoing major repairs and improvements. All funds are available until expended.

Construction of facilities for the National Institutes of Health spans a period of nearly 59 years, dating back to legislation that authorized Building 1 in June 1936. Facilities funded under this appropriation include those required for both research programs and support services at the main NIH reservation in Bethesda, Maryland, the NIH Animal Center located in Poolesville, Maryland, the Frederick Cancer Research and Development Center, Frederick, Maryland; the National Institute of Environmental Health Sciences (NIEHS) facility in Research Triangle Park, North Carolina, the Gerontology Research Center, Baltimore, Maryland; the Rocky Mountain Laboratory, Hamilton, Montana, and Primate Facilities at Perrine, Florida, New Iberia, Louisiana, and Sabana Seca, Puerto Rico.

The NIH has developed an updated master plan that was completed in December 1995 and approved in February 1996 for the Bethesda campus. The aging of the facilities and infrastructure, the development of new technologies, and the evolving biomedical research programs at NIH have required a new blueprint to guide future development on the campus. The new comprehensive master plan identifies programmatic requirements in terms of personnel and physical facilities, establishes concepts for future development and land use, buildings, utilities, open space, circulation and traffic management for the next twenty years, and illustrates how needs for laboratory and clinical research, administrative, and support space can be accommodated. An updated Master Plan for the NIH Animal Center in Poolesville is currently being developed and will be completed in the Fall of 1996.

The NIH is contending with an aging, deficient physical plant. The majority of the infrastructure systems are 20 to 40 years old, undersized, and beyond their design life. To address these deficiencies and plan for the future, the NIH is integrating all corrective and new construction programs into a comprehensive Facilities Revitalization Program. The intent of this program is to develop a long-term strategy to coordinate construction and renovation projects and set priorities. The purpose is to support ongoing laboratory and clinical research, anticipated technological advancements and evolving research programs with safe, functional, and adaptable modern facilities for the foreseeable future.

While the NIH gives a high priority to all safety and health requirements, it has placed the highest priority on the renewal of the Clinical Center. In addition to patient related research, the Clinical Center contains approximately 40 percent of the research space on the Bethesda campus and is the keystone of the NIH Intramural Research Program. However, the utility systems within the complex are deteriorated, outmoded, obsolete, and insufficient to support modern research. The NIH has developed plans to renew the complex in accordance with the recommendations contained in the External Advisory Report, the Intramural Research Program. Plans for the new Clinical Research Center (CRC) are described under Program Activities.

In addition to the CRC, the Essential Safety and Health Improvement initiative will address the necessary infrastructure upgrades of existing NIH facilities to meet critical occupational and environmental requirements to protect and support ongoing research programs, and the safety and health of NIH employees and patients. Supporting utilities will be modernized and improved to meet safety and health standards and specific requirements in support of the NIH research mission.

Purpose and Method of Operation

Funding for Buildings and Facilities during the last five years has been as follows:

<u>Year</u>	<u>Amount</u>
FY 1992	101,840,000
FY 1993	108,731,000
FY 1994	111,039,000
FY 1995	114,120,000
FY 1996	146,151,000

The Buildings and Facilities appropriation funds two major requirements of the NIH biomedical research mission: the design and construction of new facilities for NIH research programs and the continuing renovation, alteration, maintenance, and repair of existing facilities. Long-term projects currently under construction include campus infrastructure modernization, modernization/safety upgrades of the NIH Clinical Center, rehabilitation of the campus' oldest laboratory buildings, the asbestos abatement program, the fire safety and life protection program, the renovation of existing animal facilities, and construction for replacement of leased facilities at the National Institute of Environmental Health Sciences.

Overall Budget Policy

The 1997 budget request of \$420,000,000 reflects the high priority placed on safety and health requirements necessary to meet critical infrastructure and environmental improvements to the existing facilities to protect and support ongoing research programs. Funds of \$310,000,000 are included for the highest priority project for construction of the new Clinical Research Center. The enhanced program for essential safety and health improvements includes funding for the upgrade or replacement of essential equipment and systems to keep the existing Clinical Center building safely operational, the site infrastructure modernization program; the continuation of programs for power plant safety, asbestos abatement, fire protection and life safety, the elimination of barriers to persons with disabilities, a medical pathological waste system, safety and reliability upgrades at the Rocky Mountain Laboratory; implementation of an indoor air quality improvement program; and the rehabilitation of Building 6/6A. The request also provides funding for ongoing repair and improvement of facilities.

Buildings and Facilities

Program Activities

Authorizing Legislation - Section 402(b) of the Public Health Service Act

Budget Authority:

1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
\$114,120,000	\$146,151,000	\$420,000,000	+\$273,849,000

Rationale for the Budget Request

The FY 1997 budget request for Buildings and Facilities is \$420,000,000, an increase of \$273,849,000 over FY 1996. The basic thrust of the 1997 budget request is the program of essential safety and health improvements required to meet critical infrastructure and environmental improvements to existing NIH facilities in order to protect and support ongoing research programs.

I. Clinical Research Center Addition

FY 1997 Budget Request \$310,000,000

The Clinical Center is the heart of the NIH intramural program where many basic science discoveries are translated into clinical applications that address the Nation's health needs. The Center is the working environment for an unparalleled confluence of basic and clinical researchers with a breadth of expertise across many disciplines and diseases. The resulting combination of intellectual and physical resources fosters quick and formidable responses to new research opportunities and to emerging public health problems.

Each year, an average of 20,000 children and adults from across the country, and in some instances the world, are referred to the Clinical Center for experimental treatment and study. These patients account for approximately 72,000 in-patient days and 73,000 outpatient visits each year. This represents approximately 50 percent of the research days and 27 percent of the research outpatient visits supported by NIH throughout the United States. Nearly 1,000 clinical research protocols are ongoing at the Clinical Center at any one time. A heavy emphasis on Phase I and Phase II clinical trials and on studies of the pathogenesis and natural history of disease distinguishes the research mix at the Clinical Center from that of teaching hospitals, where emphasis is more on Phase III and IV clinical trials. For these

reasons, the Clinical Center is widely recognized as a unique resource for the Nation and the world.

This unique research hospital and clinical laboratory facility needs to be replaced immediately. The entire complex is rapidly approaching the end of its service life. To date, major system failures, which might harm life and/or destroy years of irreplaceable research, have been avoided only through vigilant facilities management.

The existing building complex is outmoded and functionally obsolete. Originally built in the early 1950's, the building's life safety systems and basic organization were designed to conform to standards of operation, research, and health care delivery that have long since been eclipsed by current practice. The mechanical and electrical systems have neither the capacity nor the sophistication to adequately support current research. Available air quantities and qualities are substandard. Portions of the dynamic systems (fans, pumps, etc.) have failed or are failing. The static systems (piping, ductwork, wiring, etc.) are subject to intermittent ruptures, which are both dangerous and costly to repair. At best, all these systems have a remaining life expectancy of 12 to 15 years.

The existing complex also is overcrowded. The severe overcrowding in research laboratory areas has created potentially unsafe conditions and significantly compromised the research environment. This shortage of space has virtually prevented the reconfiguration of laboratories to meet new research initiatives and congressional mandates.

During the late-1980's, it became apparent that the Clinical Center's ability to provide ongoing patient care and research activities in a safe and reliable facility was being threatened by overcrowding and a deteriorating, inadequate utility infrastructure. In 1989, an in-house review of the facility revealed a pressing need for comprehensive building improvements. In 1991, the appropriateness of this approach was validated by an independent analysis mandated by Congress and conducted by the U.S. Army Corps of Engineers. The Corps confirmed the extent and severity of the problems in the existing Clinical Center and strongly recommended immediate and major corrective action. Subsequently, the NIH undertook a series of studies including formal cost-effectiveness analysis to explore the most effective solution to providing the requisite clinical research environment on the campus.

In 1994, the External Advisory Committee of the Director's Advisory Committee, NIH, concluded that the NIH's needs could be met most efficiently by building a new facility immediately adjacent to, and integrated with, the existing structure. This new facility would replace the existing 500-bed patient care complex with a new, state-of-the-art, 250-bed hospital connected to new laboratory space. In this approach, called the Clinical Research Center (CRC), the entire research hospital and patient care programs would be relocated to a new, 600,000 gross square foot facility which will be served by additional new space dedicated to laboratory and program support space. This new, state-of-the-art complex will be located immediately north of the existing building complex. Following the completion and occupancy of the new addition, the existing building complex would be renovated in

stages. It is estimated that the new addition will take six years to complete and will be ready for occupancy in 2002.

The NIH, in conjunction with the Office of the Secretary of the Department of Health and Human Services (DHHS), explored alternate ways to complete the proposed Clinical Center Renewal project within anticipated appropriation ceilings consistent with the Administration's budget policy. Six funding options were studied in depth. After careful consideration with OMB, it was determined that a single direct appropriation that fully funds the Clinical Research Center is most appropriate for this critical project.

Funds provided in the FY 1995 appropriation were used to investigate and evaluate different project development approaches and design options for the new facility. They were also used to pay for an international design concept competition. The FY 1996 budget level includes funds for architecture and engineering design and design development for the project.

The 1997 President's Budget request includes funds required to carry the Clinical Center Renewal project forward to completion. More specifically, this request will provide for the completion of the construction documents, demolishing Building 20, preparing the site, installing the infrastructure support, and completing the construction of the new addition inclusive of associated fees for construction and project management.

II. Essential Safety and Health Improvements

FY 1997 Budget Request \$84,100,000

1. Clinical Center Essential Maintenance and Safety Program

FY 1997 Budget Request \$11,100,000

The Clinical Center Essential Maintenance and Safety (EMS) Program provides for the urgently needed restoration of the primary utility systems and the correction of specific life safety deficiencies. This is the minimum investment required in the existing Clinical Center building, until the completion of the new CRC, and for the next 12 to 15 years. The original planning and construction of the Clinical Center occurred over 40 years ago. Extensive alterations are necessary to comply with safety requirements and allow modern procedures, equipment, and facilities to provide quality patient care and supporting research. The EMS Program will focus on safety issues, hospital accreditation, and major central system renovations to enhance reliability. Implementation of the Clinical Center EMS Program has been a crucial interim project for insuring a safe and functional facility for clinical and biomedical research until the Clinical Research Center Renewal Program is completed. The EMS Program will only repair or replace essential equipment and systems, minimizing additional facility investments. This request represents the final phase of funding to complete the EMS

Program. It will provide for the completion of the restoration of smaller heating ventilating and air conditioning (HVAC) equipment distributed within the lower levels of the building. It will also provide for needed improvements of fire safety conditions, and correct emergency power deficiencies.

2. Infrastructure Modernization Program

FY 1997 Budget Request \$43,100,000

This is a continuation of the program of replacement and expansion of central utility equipment and distribution systems. The majority of the NIH Central Utility Plants and distribution networks are over 40 years old. Obsolescence and system deteriorations due to age, overburdening from growth, and increasing demand due to program needs have produced a critical situation where sufficient and uninterrupted services to research and patient care activities can no longer be ensured. The possibility of catastrophic failure has become very real. Without this program, we could no longer ensure the infrastructure capability to carry out the NIH mission.

To address this, a program plan for the restoration, renovation, replacement, and expansion of the central utility systems has been developed. Specific central utility services include chilled water, steam, electrical power, compressed air, domestic water, sewerage, and natural gas. Equipment includes chillers, boilers, control and monitoring systems, pumps, switchgear, and other ancillary apparatus. Facility accommodations include the necessary conversion, expansion, or creation of mechanical and electrical system spaces, as well as any program relocations which are a result of this effort.

The FY 1997 increment, which is the seventh of a nine-year program, will continue the replacement and/or enhancement of specific central utility equipment and systems which have been identified as mandatory to maintain current campus-wide operations. Work of this phase will include expansions of the refrigeration building to house secondary pumping apparatus, chillers, additional electrical equipment and controls for the chillers and boilers in the Power Plant. Funds will be used to continue construction of a new utility distribution tunnel for underground chilled water and steam distribution piping service, and to replace storm, electrical, potable water and sanitary systems.

3. Power Plant Improvements

FY 1997 Budget Request \$2,900,000

This program provides for the necessary modifications to the NIH Power Plant to enable continuing emissions compliance with National Ambient Air Quality Standards. This is the fourth year of a five-year program for upgrading the NIH Power Plant, Building 11, to maintain and improve emissions in compliance with acceptable air quality standards. The requested funding will continue the installation of flue gas recirculation devices and removal of hazardous materials from within the Power Plant.

4. Asbestos Abatement Program

FY 1997 Budget Request	\$6,000,000
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This project provides for the continued phased removal of asbestos containing materials from various NIH buildings. Insulation, fireproofing, and ceiling and wall finishes containing asbestos are present in virtually all NIH buildings. Disturbed or deteriorating asbestos fibers can be released into the air, risking the health of those persons exposed. Asbestos control practices are instituted whenever there is a risk of exposure to significant airborne asbestos concentrations. Most building renovation activities involve asbestos abatement as part of the overall renovation effort. In some cases, the costs associated with asbestos abatement are a substantial part of the total cost of construction and renovations. This is the fourth year of a ten-year program.

5. Fire Protection and Life Safety Program

FY 1997 Budget Request	\$2,000,000
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Funding is requested for the fourth year of a multi-year program to upgrade the fire protection and life safety equipment of NIH buildings on the campus and at the NIH Animal Center. Significant deficiencies exist which could compromise NIH's ability to provide full and adequate protection to all persons using or working in NIH facilities as well as protection of critical research facilities and resources. A master fire protection plan has been developed as part of the program. Fire sprinklers and an improved fire alarm reporting system will be installed. The program will achieve improvements in emergency egress, as well as upgrading of fire doors, door hardware, emergency lighting, and exit marking.

6. Eliminate Barriers to Persons With Disabilities

FY 1997 Budget Request	\$1,500,000
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This is a continuation of the program to systematically remove existing barriers on the interior of NIH buildings. A survey of NIH buildings has been completed which identifies access barriers as well as remaining architectural barriers. Items that still need modification, such as additional restrooms, elevator controls, door openings, and fire alarm devices are being developed in concert with the NIH Employees with Disabilities Committee. Eliminating barriers in exterior situations has been largely satisfied, or in progress.

7. Medical Pathological Waste Management System

FY 1997 Budget Request \$2,500,000

This project provides for the acquisition, construction and implementation of a medical pathological waste (MPW) system. A study is being conducted to determine the best alternative to incineration for the disposal of medical waste at the NIH. The goal is to provide a medical waste handling system to be implemented in either a centralized location or two to three decentralized locations on the NIH campus or possibly a remote location. The scope of the project includes site preparation, purchase of capital equipment, building fit-out, permit preparation, regulatory testing, construction, installation, and project management.

8. Safety and Reliability Upgrades, Rocky Mountain Laboratory

FY 1997 Budget Request \$9,300,000

Funds are requested to support the major portion of the fourth year of a five-year program to upgrade the existing main laboratory complex at the Rocky Mountain Laboratory in Hamilton, Montana, to be compliant with current fire/life safety standards for biomedical research facilities. The safety and reliability upgrades include the replacement of piping; addition of heating, ventilation, and air conditioning systems; an increase in electrical services; the construction of a central utility plant necessary for consolidating new mechanical, electrical, and infrastructure elements; structural bracing against increased seismic activity; installation of a fire sprinkler system throughout the complex; and other modifications required for code compliance and accessibility. These funds will provide for the upgrade of all six buildings of the main laboratory complex and the completion of life safety and utility upgrades of the other vivarium and support buildings.

9. Indoor Air Quality Improvement Program

FY 1997 Budget Request \$1,500,000

This is a multi-year program for the study, design, and construction to fully address indoor air quality concerns at NIH facilities. This program allows for the evaluation of existing structures and ventilation facilities to determine the total need for system upgrades or replacements. Items of concern to be evaluated include heating, ventilation, and air conditioning system capacity; relative air flow; fume hood operation; recirculated air quality; sources of contamination; and potential cross-contamination. A comprehensive program will be developed to fully address the indoor air quality requirements.

10. Modernization of Building 6/6A

FY 1997 Budget Request	\$4,200,000
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This request provides for the initial funding for the design of the rehabilitation of Building 6 and the partial upgrade of Building 6A. The rehabilitation of Building 6, a historic structure and the oldest operational laboratory building on the NIH Bethesda campus, will be accomplished through complete renovation, and possibly a new addition, in order to meet current safety and reliability standards for biomedical research. Such modernization is necessary since the aged building infrastructure has become unreliable requiring that a moratorium be imposed on all scientific equipment and any interior building modifications. The Building 6 and 6A renovations would include the removal of asbestos; replacement of aged, deteriorated mechanical, electrical and piping equipment; improvement in piping distribution of main building systems; modernization of elevators; upgrading laboratory and laboratory support spaces; architectural changes to meet current accessibility requirements; inclusion of fire sprinklers; and refurbishing of interior and exterior finishes.

III. Repairs and Improvements

FY 1997 Budget Request	\$25,900,000
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The Repairs and Improvements (R&I) program provides for major repairs and improvements to the physical plants at Bethesda, Poolesville, Baltimore, and Frederick, Maryland; Research Triangle Park, North Carolina; Hamilton, Montana; Perrine, Florida, and other field stations for which NIH has the property-holding responsibility. The costs for some of the projects are recurring and substantial. For example, some projects such as roofs, roads, structures, and building and underground utilities require ongoing repairs and maintenance to preserve or achieve reliable and safe conditions. For other projects, the costs are largely one-time, often unpredictable expenditures for major items of equipment requiring emergency repair or replacement such as transformers, chillers, and cooling towers. Specifically, the following projects are planned: correct the HVAC system deficiencies in laboratory Buildings 36 and 29A which are beyond their useful life; replace electrical disconnects in the Building 31 electrical vaults; continue major repairs to structural systems of parking structures of the ACRF and Garages 6 and 7; replace deteriorated roofing on several animal and research laboratory buildings; clean the potable water distribution system; continue major upgrade of outdated Bethesda campus elevators; provide chiller consolidation and improve electrical services at the NCI-FCRDC to meet reliability requirements; and replace high temperature hot water generators at the NIEHS.

In addition, this program supports adjustments to the infrastructure utility systems to provide necessary capacity to accommodate changes in the direction of research. These repairs or replacements require immediate attention, and thus are not suited to a schedule of expenditures such as found in the Infrastructure Modernization Program. To be consistent with the 1990 report by the National Academy of Sciences (NAS), "Committing to the Cost of Ownership, Maintenance and Repair of Public Buildings," the total calculated budget for repairs and maintenance for all NIH facilities in FY 1997 would be \$102.5 million, including routine and deferred maintenance requirements. While the routine maintenance of NIH facilities is funded by operating funds, the remaining portion of the NAS recommended maintenance and repair funding, in the amount of \$83.6 million, would otherwise be provided by the R&I program. The FY 1997 R&I request of \$25.6 million represents our continued efforts to provide sufficient and appropriate annual R&I funding as outlined by the NAS guidelines.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Project

(Dollars in thousands)

	1995	1996	1997	
	Actual	Estimate	Estimate	Change
Clinical Center Essential Maintenance and Safety Program	\$20,000	\$21,000	\$11,100	-\$9,900
Infrastructure Modernization Program	13,439	13,800	43,100	+\$29,300
Power Plant Improvements	2,000	2,000	2,900	+900
Asbestos Abatement Program	5,500	5,500	6,000	+500
Fire Protection and Life Safety Program	2,000	2,000	2,000	—
Eliminate Barriers to Persons With Disabilities	—	1,500	1,500	—
Safety and Reliability Upgrades RML	2,000	4,700	9,300	+4,600
Medical Pathological Waste Management System	3,500	—	2,500	+2,500
Indoor Air Quality Improvement Program	—	1,500	1,500	—
Modernization of Building 6/6A	—	—	4,200	+4,200
New Fire Station	—	5,570	—	-5,570
Clinical Research Center Renewal Program	—	23,000	310,000	+287,000
Consolidated Laboratory Building	30,800	34,754	—	-34,754
William H. Natcher Building	17,381	19,427	—	—
Repairs and Improvements	10,000	6,000	25,900	+6,473
NIEHS Additions to Facilities	5,000	5,400	—	-6,000
Turner Construction Claims, North Carolina	2,500	—	—	-5,400
Clinical Center Review	—	—	—	—
Cell Biology Facility	—	—	—	—
Total budget authority	114,120	146,151	420,000	+273,849
Unobligated balance, start of year	245,073	141,510	—	-141,510
Unobligated balance, end of year	-141,510	—	—	—
Total obligations	217,683	287,661	420,000	+132,339

Buildings and Facilities

Summary of Changes

1996 Estimated budget authority	\$146,151,000
1997 Estimated budget authority	<u>420,000,000</u>
Net change	+273,849,000

Change from
Base Budget
Authority

Increases:A. Program:

1. Infrastructure Modernization Program	+29,300,000
2. Power Plant Improvements	+900,000
3. Asbestos Abatement Program	+500,000
4. Medical Pathological Waste Management System	+2,500,000
5. Safety and Reliability Upgrades, RML	+4,600,000
6. Modernization of Building 6/6A	+4,200,000
7. Clinical Research Center Renewal Program	+287,000,000
8. Repairs and Improvements	<u>+6,473,000</u>

Total increases +335,473,000

Decreases:A. Program:

1. Clinical Center Essential Maintenance and Safety	-\$9,900,000
2. New Fire Station	-5,570,000
3. Consolidated Laboratory Building 50	-34,754,000
4. NIEHS Additions to Facilities	-6,000,000
5. Turner Construction Claims, NIEHS	<u>-5,400,000</u>

Total decreases -61,624,000

Total, Net Change +273,849,000

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Object

	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>	<u>Increase</u> <u>or</u> <u>Decrease</u>
Other Services	\$146,151,000	\$420,000,000	+\$273,849,000
(Obligations)	<u>(287,661,000)</u>	<u>(420,000,000)</u>	<u>(+132,339,000)</u>
Total budget authority by object	146,151,000	420,000,000	+273,849,000
(Total obligations by object)	(287,661,000)	(420,000,000)	(+132,339,000)

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Clinical Research Center Renewal Program - ... The House in its report 104-209, page 83, states, "The Committee is aware that NIH is considering a number of options to finance and construct a new clinical center hospital facility. The Committee expects to be notified of NIH's plans regarding design and construction, both immediate and long-term, as well as financing, before any financial or contractual commitments are made to begin the project."

Action Taken or to be Taken

The FY 1997 budget request provides for full funding of the entire construction cost of the facility.

1996 Senate Report LanguageItem

Clinical Research Center Renewal Program- ... The Senate in its report 104-145, page 115, states, "The Committee notes that the NIH is still reviewing several options to finance and construct a new clinical center on the NIH campus. The Committee concurs with the House directive that it be notified of NIH's plans regarding design and construction, before any commitments are made to begin the project."

Action Taken or to be Taken

The FY 1997 budget request provides for full funding of the entire construction cost of the facility.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Authorizing Legislation

Funded Authorizations: Buildings and Facilities	PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Estimate
Title IV, Section 402(b)		405282	Indefinite	\$146,151,000	Indefinite	\$420,000,000
Total Budget Authority				146,151,000		420,000,000

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u>	<u>1/</u>
1987	\$8,000,000	\$31,900,000	\$31,900,000	\$31,900,000	
1988	5,000,000	30,000,000	50,000,000	47,870,000	
1989	5,000,000	20,000,000	12,500,000	38,532,000	
1990	21,600,000	81,600,000	41,600,000	61,600,000	
1990 Sequester				-558,000	
1991	86,903,000	239,903,000	68,603,000	168,687,000	2/
1991 Sequester				-2,000	
1992	104,125,000	108,625,000	89,485,000	103,840,000	
1993	72,518,000	70,090,000	59,222,000	108,731,000	
1994	108,731,000	114,385,000	101,000,000	111,039,000	
1995	113,539,000	114,370,000	113,370,000	114,120,000	3/
1996	144,120,000	146,151,000	140,384,000	146,151,000	
1997	420,000,000				

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes enacted administrative reduction of \$4,166,000.

3/ Excludes enacted rescission of \$60,000,000 of prior year unobligated balances.

THURSDAY, APRIL 25, 1996.

OFFICE OF THE DIRECTOR

WITNESSES

DR. RUTH KIRSCHSTEIN, M.D. DEPUTY DIRECTOR

DR. HAROLD VARMUS, M.D., DIRECTOR

DR. WILLIAM HARLAN, M.D. ASSOCIATE DIRECTOR FOR DISEASE PREVENTION

ANTHONY ITTEILAG, DEPUTY DIRECTOR FOR MANAGEMENT

STEPHEN A. FICCA, ASSOCIATE DIRECTOR FOR RESEARCH SERVICES

DR. MICHAEL GOTTESMAN, M.D., DIRECTOR, OFFICE OF INTRAMURAL RESEARCH

DR. WENDY BALDWIN, M.D., DIRECTOR OF EXTRAMURAL ACTIVITIES AND

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. ISTOOK. Dr. Kirschstein.

OPENING STATEMENT

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman.

I'm delighted to present to you the programs, in summary, of the Office of the Director. Over the past year, we've had a revitalization, and we are pleased that all of our programs in the Office of the Director are working cooperatively and in excellent collaboration, not only among themselves, but with the various institutes, centers and divisions. It is particularly important in an era of constraint that all our activities are performed as efficiently and effectively as possible.

Now, as you know, complex medical problems require us to call upon various scientific disciplines and to coordinate diverse approaches to avoid duplication of effort, and to ensure that the most important leads are followed. The specially designated offices and programs of the Office of the Director were specifically established to provide such coordination. And the directors of those programs and offices are here with us today. They will be pleased to answer any specific questions that you may have.

OFFICE OF DISEASE PREVENTION

Let me describe some of these major programs. The Office of Disease Prevention has the responsibility to coordinate prevention research throughout NIH. As part of this effort, a new Office of Dietary Supplements was established this year to support studies and to interact with the researchers and programs related to nutrition in the various institutes and centers.

OFFICE OF RARE DISEASES

We also have an Office of Rare Diseases. Now, you heard a great deal about rare diseases, as we were discussing the issue related to the clinical research in the buildings and facilities testimony. And there is, of course, research on rare diseases done outside of the clinical center, although, as Dr. Varmus said, there is a concentration of efforts there.

This unit coordinates the necessary collaborative efforts regarding these diseases, which are so rare that, as we said, no one scientist can work alone, and patients must band together, so that there are sufficient numbers for clinical studies. In order to facilitate such research, an on-line data base is being established. That not only allows the patients and their families to have interactions with each other and come together to know what's going on, but it also allows physicians throughout the country to know what is going on and what are the latest findings concerning rare diseases.

Two other offices address specifically research regarding our special populations, minorities and women. Unfortunately, the minority population at nearly all stages of life suffers poorer health and higher rates of premature death than do members of majority populations. And so there is a minority health initiative which is funding projects related to high rates of infant mortality and low birth weight, treatment of asthma, which is much higher in minority populations, lead exposure in childhood, and the leading causes of infectious disease which impede childhood development. That office also supports research training for disadvantaged students.

OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health serves to identify emerging scientific opportunities to close the gaps in knowledge about women's health. These are gaps which affect both mortality and morbidity. The Women's Health Initiative, which has been described to this committee over several years, is a 15 year project involving 164,000 women aged 50 to 79. It focuses on strategies for preventing heart disease, breast and colorectal cancer and osteoporosis, all of which cause death, disability and frailty in older women.

I am pleased that the initiative continues to be on budget, and that the enrollment of minority women in these projects, because these women are particularly vulnerable, is nearing 88 percent of the goal.

OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

Two other offices are of special note. The Office of Behavioral and Social Sciences Research was established by legislation to coordinate research regarding behaviors such as smoking, dietary practices, lack of physical activity, stress, alcohol and drug abuse, accidents and socioeconomic status. These are risk factors for an array of health problems.

OFFICE OF ALTERNATIVE MEDICINE

The Office of Alternative Medicine provides a central NIH focus regarding complementary medical practices. In the year 1990, for

example, in the United States, one out of every three Americans saw an alternative health care practitioner, and \$13 billion was paid for these services. The Office of Alternative Medicine, therefore, was established to facilitate scientific evaluation of these medical treatment modalities.

Mr. Chairman, all of these activities of the Office of the Director add to the ability of the NIH overall to foster and support its mission of research that will improve the health and well-being of all the segments of the American public. The appropriation request for the Office of the Director is \$226,913,000. I'd be pleased to answer your questions.

[The prepared statement and biography of Dr. Ruth Kirschstein follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Deputy Director of the
National Institutes of Health
Office of the Director

We are pleased to have this opportunity to be here today to discuss with the Committee the FY 1997 Budget for the Office of the Director (OD). In doing so, as last year, it is important to articulate the principles by which the Office of the Director operates. This Office provides leadership, coordination and policy direction for both the overall extramural and intramural research and research training programs of the various Institutes, Centers, and Divisions (ICDs) as well as the special offices within the immediate Office of the Director. The OD also provides management leadership and centralized support activities essential to the operation of the National Institutes of Health (NIH).

The complex medical and scientific issues and research problems described during these hearings require many avenues of inquiry--calling upon various scientific disciplines and involving laboratory research, the social and behavioral sciences, clinical studies, and epidemiologic approaches. As the technology to perform such research has become more sophisticated and more interdisciplinary approaches are required, coordination is necessary to avoid duplication of effort and to ensure that the most meritorious leads are followed. With such coordination, we hope to continue to fulfill the expectations of the American people and the Congress that the funds provided to NIH will be efficiently and effectively used to improve health and decrease the burden of disease and disability. Many of these coordinated efforts are focussed in the OD and are the responsibility of specially designed offices and programs.

The Office of Disease Prevention

Maintenance of health and prevention of disease are critical to the length and quality of life. All of NIH's institutes and centers have programs in prevention research, ranging from studies to understand normal physiology to clinical trials on diet modification to health education programs aimed at the public. These are coordinated by the Office of Disease Prevention which was established ten years ago.

This past year, a new Office of Dietary Supplements (ODS) was established as part of the NIH disease prevention activities. It will support research related to dietary supplements, their health benefits and their role in disease prevention. The new Director of ODS will expand opportunities to interact and exchange information with staffs of the Institutes and Centers and with researchers throughout the country. In addition, the office will compile a database regarding the results of research related to dietary supplements.

Another part of the disease prevention activities concerns rare diseases--those diseases having a prevalence of 200,000 or fewer cases in the U.S. The Office of Rare Diseases Research is collaborating with the institutes and centers as well as advocacy groups to develop a publicly available on-line database that will provide sources of information to and about support groups, as well as current research projects and the names of the investigators working on these projects.

Office of Behavioral and Social Sciences Research (OBSSR)

Behavioral and social factors, such as smoking, dietary practices, lack of physical activity, stress, alcohol and drug abuse, accidents, unsafe sexual

practices, and socioeconomic status are well documented as risk factors for an array of health problems. The new Office of Behavioral and Social Sciences Research is preparing a trans-NIH plan and initiatives to stimulate research and promote studies across all of the NIH so as to evaluate the contributions of behavioral, social and lifestyle determinants in the development, course, treatment, and prevention of illness and related public health problems.

Office of Research on Women's Health (ORWH)

The budget request for ORWH not only will allow that office to continue its role as the focal point for women's health research across NIH, but to identify emerging scientific opportunities not previously defined or recognized as well as the continuing gaps in knowledge about women's health, gaps which affect both mortality and morbidity. The ORWH will continue to develop programs that assist and guide women (and minorities) into biomedical research careers.

The Women's Health Initiative

The Women's Health Initiative (WHI), a \$628 million, 15-year project involving 164,500 women aged 50-79, is a trans-NIH activity which focuses on strategies for preventing heart disease, breast and colorectal cancer, and osteoporosis, all of which cause death, disability, and frailty in older women of all races and socioeconomic backgrounds. I am pleased to report that the Initiative continues to be on budget, and that enrollment of minority women is nearing 88 percent of our goal.

The Office of Research on Minority Health

Minorities at nearly all stages of life suffer poorer health and higher rates of premature death than do members of the majority population. The budget request for the Office of Research on Minority Health (ORMH) and the Minority Health Initiative (MHI) provides continued funding for a series of multi-year research studies aimed at improving the health of minority populations, developing protocols for intervention in health behaviors which affect the longevity and quality of life for minorities, as well as continuing existing programs preparing minority scientists for careers in biomedical sciences. Building on previous successes, the MHI will fund a series of projects that foster a better understanding of the determinants leading to high rates of infant mortality and low birth weight, support studies on the treatment of asthma, on lead exposure in childhood, and on the leading causes of infectious diseases which impede childhood development.

The Office of Alternative Medicine

The Office of Alternative Medicine (OAM) provides a central NIH focus regarding complementary medical practices. Alternative medical practices are becoming increasingly popular in the industrialized world, and it is expected that research might help in identifying effective approaches.

The mission of the OAM is to facilitate the scientific evaluation of alternative medical treatment modalities; to investigate and evaluate the efficacy of alternative treatments; to establish an information clearinghouse for the public; and to support research training in alternative medical practices. The budget request for the OAM provides funds to continue support for 10 national clinical research centers that conduct alternative and complementary medicine research. In addition, the OAM will continue its collaborative funding of on-going alternative medical studies supported by the various NIH ICs, support a public information clearinghouse, and develop a database to disseminate information about useful complementary practices.

Other OD Activities

- . To improve education of the public in science, the NIH Office of Science Education (OSE) is a central focus for the coordination of the activities of all the Institutes, Centers, and Divisions and provides a number of outreach programs such as a Science in the Cinema film festival. The NIH loan repayment and scholarship programs are part of this office.
- . The Office of Communications provides science-based health information and is currently piloting a television program called "Health Week".
- . Other offices help to set science policy, advise the Director regarding legislative issues, assure that all NIH personnel have equal employment opportunities and provide liaison with the Bethesda neighborhood communities. Other OD entities provide leadership in regard to the overall intramural, extramural and management activities of NIH, setting policies and assuring that components of NIH effectively and efficiently fulfill their missions.

In conjunction with the recommendations of the National Performance Review, the OD continues to make organizational realignments consistent with the goal of streamlining operations. Since FY 1994, the OD has been successful in eliminating numerous headquarters positions, delegating authorities to lower levels in the organization, increasing supervisory-to-employee ratios in some offices to 1:11 and eliminating a number of substructures in other offices. In FY 1997 the OD plans to continue the assessment of its organizational structure to further align and streamline activities and to increase the use of technology to improve efficiency. The OD will also continue and expand partnerships with other NIH components to share resources.

The FY 1997 budget request for the Office of the Director is \$226.9 million. I would be happy to answer questions.

CURRICULUM VITAE
RUTH L. KIRSCHSTEIN, M.D.

POSITION: Deputy Director, National Institutes of Health

BIRTHPLACE and DATE: Brooklyn, New York
 October 12, 1926

EDUCATION: B.A., magna cum laude, Long Island University, 1947
 M.D., Tulane University School of Medicine, 1951

EXPERIENCE: Acting Director, National Institutes of Health, July-November, 1993
 Director, National Institute of General Medical Sciences, NIH, 1974-1993
 Acting Associate Director for Research on Women's Health, NIH, 1990-1991
 Deputy Associate Commissioner for Science, FDA, 1973-1974
 Acting Deputy Director, Bureau of Biologics, FDA, 1972-1973
 Assistant Director, Division of Biologics Standards, NIH, 1971-1972
 Chief, Laboratory of Pathology, DBS, NIH, 1965-1972
 Acting Chief, Laboratory of Pathology, DBS, NIH, 1964-1965
 Assistant Chief, Laboratory of Viral Immunology and Chief, Section of Pathology, DBS, NIH, 1962-1964
 Chief, Section of Pathology, Laboratory of Viral Immunology, DBS, NIH, 1960-1962
 Medical Officer, Pathologist, Laboratory of Viral Products, DBS, NIH, 1957-1960
 Medical Officer, Resident in Pathology, Clinical Pathology, Clinical Center, NIH, 1956-1957

CERTIFICATION: Medical Specialty Board Certification, Pathology (anatomic and clinical pathology), 1957

SPECIAL AWARDS or CITATIONS: Public Service Award, Federation of American Societies for Experimental Biology, 1993
 Elected as a Fellow of the American Academy of Arts and Sciences, 1992
 Honorary Doctor of Humane Letters, Long Island University, 1991
 Dr. Nathan Davis Award (American Medical Association), 1990
 Office of Personnel Management Profiles in Excellence, 1989
 Presidential Distinguished Executive Rank Award, 1985
 Honorary Doctor of Laws, Atlanta University, 1985
 Distinguished Executive Service Award of the Senior Executive Association, December 1985 and 1995
 Georgeanna Seegar Jones Women's Health Lifetime Achievement Award, June 1995

COMMITTEE MEMBERSHIPS: Co-chair, PHS Coordinating Committee on Women's Health Issues, 1990-present
 Member, Interagency Working Group on Minorities, Women and the Handicapped in Science, 1989-1991
 Chairperson, NIH Working Group on Minorities in Biomedical Research, 1988-1989
 Member, Federal Task Force on Women, Minorities and the Handicapped in Science and Technology, 1987-1990
 Chairperson, PHS Coordinating Committee on Women's Health Issues, 1985-1990
 HHS Executive Development Board, 1985-present

March 1996

BUDGET DECREASE

Mr. ISTOOK. Thank you, Doctor. And you didn't point it out, but of course, as you know, the budget request is a 3.4 percent decrease.

Dr. KIRSCHSTEIN. That's correct.

POLICY-ORIENTED OFFICES

Mr. ISTOOK. And obviously I and members of this subcommittee and others always appreciate the efforts that go into doing such things. Because we all know the job we have ahead of us.

I have a copy of a simplified office organization chart. And in the administrative structure of the Office of the Director, there are a number of the policy oriented offices. You touched upon them. Considering that your administrative structure, your offices, includes those units, as they do, how many people actually, perhaps this really ought to go to Dr. Varmus, how many people are actually reporting directly to you on a regular basis?

Dr. VARMUS. Fourteen altogether.

Mr. ISTOOK. Okay, 14 of that, and then it breaks down, I think the total number in the office is something like 749 FTE, if I recall right.

Dr. VARMUS. Approximately.

Dr. KIRSCHSTEIN. Yes.

Mr. ISTOOK. Okay. Now, in the policy offices, and you have outlined in your budget flow of money that technically is denominated, it's coming to the Office of the Director but then flows through to these different entities, do these policy offices then actually award the research grants? And I'm talking about the policy offices in the Office of the Director, or do they funnel their money to the institutes where the awards are actually made?

Dr. KIRSCHSTEIN. The policy offices do not make any awards. Indeed, the Office of the Director makes no direct research grant awards. All of the efforts are coordinated with the institutes and depending on which institute is most involved in the monies will be then transferred from the program offices that are dealing with women's health or minority health to that institute and the institute will make the awards.

OD FUNDS THAT SUPPORT ICDS

Mr. ISTOOK. In your budget justification, of course, you show this as far as appropriations and then funds that are reimbursed or directly support the institutes. To us, we look at it, and it's just a couple of lines on a piece of paper. But when you have this as part of your accounting system, is there some sort of process by which money is cleared from the Director's office to then flow through to the institutes?

Dr. KIRSCHSTEIN. Yes.

Mr. ISTOOK. What is that process?

Dr. KIRSCHSTEIN. Well, as the program offices work, coordinating with the institutes, and research grant applications are received that are appropriate, decisions are made together as to how much money should be provided for those studies. Each of the program offices has a budget provided to it. They decide what they can and

cannot do, and with advice from many people, they usually talk with me and some of the other people, then through the office that is run by our Director of Extramural Activities, Dr. Wendy Baldwin, arrangements are made and the financial management office arranges for the transfer.

Mr. ISTOOK. If these were expenditures of money that were already budgeted to the different institutes, why do they need to come back to a central control, basically saying, "approve what has already been approved?" I realize I may not characterize it correctly.

Dr. KIRSCHSTEIN. These are additional funds, Mr. Istook. Because over the years, many of the people on this committee and other committees felt that certain areas needed emphasis that could be better performed by coordinated efforts and be looked at through the Office of the Director, so as to fill the gaps that I mentioned before. Therefore, the money was appropriated to these offices which then had expertise to study the issues and provide the funds in coordination.

Mr. ISTOOK. Am I incorrect regarding that there is any predetermined allocation or range of allocations?

Dr. KIRSCHSTEIN. To the institute? There are no pre-arranged allocations.

Mr. ISTOOK. So conceivably, then—looking at page 149 of your justification, volume 5, there where it has, for example, 1997 estimate, and it has the breakdowns, you have the Director's discretionary funds, then you have the figures for the research on minority health, research on women's health, women's health initiative and so forth. Are those amounts that are reflected there, for example, on the minority health initiative, that is a \$62.5 million figure—

Dr. KIRSCHSTEIN. Right.

Mr. ISTOOK. Are you saying that amount is not predetermined, as reflected in the estimate here?

Dr. KIRSCHSTEIN. It's not predetermined specifically, except as a commitment to an institute that has an ongoing program. And Dr. Ruffin in that office has agreed that he will support activities, because they are important, on asthma research in minority populations, particularly in children. It is not predetermined that every year, exactly, the same amount of money will go to a particular institute.

Mr. ISTOOK. And I'm talking about the portion of the money, of course, that comes from the Director's office.

Dr. KIRSCHSTEIN. Right.

Mr. ISTOOK. It's not determined every year, but each year it is determined in advance of that fiscal year?

Dr. VARMUS. It's determined how much goes to that office. But how much of that office's money goes to individual institutes or individual projects will be determined during the course of that year.

Mr. ISTOOK. Okay, that's the allocation you're talking about. When they say, okay, here's our allocation, this to this institute, this to that institute and so forth.

Dr. KIRSCHSTEIN. Yes.

Dr. VARMUS. Right.

Mr. ISTOOK. That's the clearance process of which you speak.

Dr. KIRSCHSTEIN. Yes.

Dr. VARMUS. I should also mention, Mr. Istook, that each of these offices has been encouraged to develop an advisory board of outside consultants who are expert in these areas to help decide which of the applicants from the institutes for supplemental funding would be successful.

PERSONNEL REQUIRED TO APPROVE FUNDING FOR ICDS

Mr. ISTOOK. How many of the personnel through the Office of the Director are involved in this process of approving the funding through the policy offices to the various institutes? How many people are necessary for that process?

Dr. KIRSCHSTEIN. Well, you said that the total number of FTEs is 749. Now, a certain number of those are in the immediate Office of the Director, a certain number of them in the advisory structure. I would say that it's between 30 and 40 who are the people in the Office of Research on Women's Health, Office of Research on Minority Health, Office of Disease Prevention, Office of Behavioral Sciences, Office of Alternative Medicine.

Dr. VARMUS. The numbers, Mr. Istook, are right there on the same page, next to the amount.

Mr. ISTOOK. Yes, that's the total FTE in the office.

Dr. KIRSCHSTEIN. Yes.

Mr. ISTOOK. So when I ask which of those are involved in the allocation, that's what you're saying, is all of those?

Dr. KIRSCHSTEIN. Now, several of those people are support staff, secretarial.

Dr. VARMUS. Less than half.

Dr. KIRSCHSTEIN. And program analysts. The major decisions are made by the program offices directors, who are experts who were chosen because of their expertise, and who use the advice that Dr. Varmus is discussing.

Mr. ISTOOK. Okay, so it would not be all the FTE?

Dr. KIRSCHSTEIN. No.

Mr. ISTOOK. Because it certainly seems that it's a very complex process.

Dr. KIRSCHSTEIN. It is.

PRIORITIES OF POLICY OFFICES

Mr. ISTOOK. Perhaps unnecessarily so. And is there a way to try to achieve the objective of making sure that funding in the institutes reflects the priorities these policy offices have? And goes therefore to projects in those institutes? Is there a simplified mechanism that is possible for doing that?

Dr. VARMUS. Well, Mr. Istook, one way to think about this is that many of these areas, of course, are supported by much larger sums than are represented here. These are additional funds that are intended to remedy deficiencies in the past, especially with respect to minority health and women's health, and to help coordinate activities that we believe can be pursued more effectively by some centralized coordinating offices for example, there's an office for Behavioral and Social Sciences Research, and across the NIH, roughly \$800 million is being spent on research in these areas.

Mr. ISTOOK. Yes.

Dr. VARMUS. A very small amount of that money, very small, comes from this office.

Dr. KIRSCHSTEIN. I would say that one of the major activities of each of these offices is to provide direction and the coordination and to lead the institutes very often to move into areas in which there have been gaps. And in that case, then, the institutes begin to make their own priorities and spend money from their own budgets.

Dr. VARMUS. I would like to further point out that some of these goals are being reinforced by the activities of these offices. That is, in the case of the women's health office and the minority office, there's a clear charge to help recruit women and minorities into biomedical research careers and to provide information to people who seek specialized information about these topics. So there is really a diversity of activities. It's not simply an activity that's geared toward supplementation of research activities.

POLICY OFFICES NOT CREATED PURSUANT TO CONGRESS

Mr. ISTOOK. Are there any of these policy offices that are not created pursuant to Congressional direction?

Dr. KIRSCHSTEIN. Yes, sir. The offices that we've been talking about primarily are what we differentiate as program offices. For example, we have an Office of Science Policy and an Office of Communications, which are very important for providing information and providing coordination of policies that the entire NIH would set up. These are offices that have functions similar to those in other agencies, but they are not necessarily set up by—

Mr. ISTOOK. They are not involved, though, in this reallocation of funds, are they?

Dr. KIRSCHSTEIN. No. They are not.

Mr. ISTOOK. Those are the ones of which I speak. All of those—

Dr. VARMUS. I think actually there is a confusion in terminology.

Mr. ISTOOK. Certainly. Yes. Those that are involved in allocating these funds—

Dr. VARMUS. Program aspects, yes.

Mr. ISTOOK [continuing]. Programming them among the institutes, whatever is the correct terminology.

Dr. KIRSCHSTEIN. Almost all of those have been established by legislation.

Mr. ISTOOK. Okay. That's what I wanted to be certain of. Okay. Those have been. Because again, and certainly there have been efforts in the Administration and efforts in Congress, when you talk about reinventing government, on how many levels, how many layers do you need to accomplish the purpose which you seek to accomplish. And has there been any discussion or proposals, whether they were accepted or rejected, saying that if Congress permitted us to do so, we could streamline this process and still make sure that the funding objectives are being met?

Dr. VARMUS. Mr. Istook, these are really not additional layers. In other words, the vast majority of activities in the areas of women's health and minority health are being carried out at the institutes. There may be consultation, but there is no requirement for approval through these offices. So we're not talking about another layer of bureaucracy, we're talking about an instrument in the Of-

fice of the Director that helps to coordinate information, help enrich fields, and sometimes supplement research activities. But it doesn't intercede between the granting authority and the institutes and the grantees.

Mr. ISTOOK. I've got to tell you, I fail to see the distinction that you're seeking to make. Maybe some other material will help me to communicate better and understand.

Dr. VARMUS. If all grants had to be approved in the area of minority health by passing through the minority health office, then we would have another layer of bureaucracy. But that's not the way we—

Mr. ISTOOK. No, I'm not saying that all grants have to be approved in that sense. But you are talking about some funding that they make the decision on how to allocate it between the different institutes. And it's the people that are involved in that process of which I speak.

Dr. KIRSCHSTEIN. Now, for example, when the new Office of Dietary Supplements was legislated, we made the decision not to set it up as a separate office that would report directly to Dr. Varmus. And it is under the Office of Disease Prevention. And that made the issues much simpler.

WOMEN'S HEALTH INITIATIVE

Mr. ISTOOK. Okay. Can you give us an overview of the Women's Health Initiative, for example, the number of centers that have been established, the number of women recruited, and if the original hypotheses have changed?

Dr. KIRSCHSTEIN. I could do that, and would be pleased to. But I think you might want to hear from Dr. William Harlan, who has the responsibility for that project.

Mr. ISTOOK. Okay. Doctor?

Dr. HARLAN. Thank you, Mr. Istook. I'm pleased to tell you that we are, as the summary says, on budget and on schedule. We have 40 clinical centers, that are recruiting the participants in the study, one coordinating center that is handling all the data, and is coordinating all the efforts in terms of protocol and adherence to the protocol.

Right now, we have screened over 160,000 women for participation in this study. The clinical trial, which is one of the components of the study, has about 24,000 women enrolled in this study. We have an observational study, which is of women who do not wish to participate in the clinical trial but who will be followed over a period of time to determine characteristics that cause disease and also to evaluate some of the markers for those diseases. We have about 30,000 women that are enrolled in that part of the study.

We have a very active participation among all of the centers in terms of the recruitment. I'm pleased to say that the women that are enrolled are very excited about the study, as are all of the people who are conducting the study.

Mr. ISTOOK. Has there been, as you've progressed, any change in the hypotheses from which you're working?

Dr. HARLAN. No, we haven't changed the hypotheses. I think they are what I would term "durable hypotheses". The question about the benefits and risks of hormonal therapy, for example, is

a durable hypothesis. Until we have information from the clinical trial we will not have full information.

The issue about diet and its ability to prevent breast cancer, colorectal cancer and heart disease I think again is a durable hypothesis. Despite reports that are released from time to time, we still don't have a clinical trial that will allow us to make a clear distinction about the value of diet for those three conditions.

Similarly, we could say that about osteoporosis and the use of calcium and vitamin D as a supplement. Without a large clinical trial in this age group of women, I don't think we can make the kinds of public health statements that are needed about the use of supplements.

Mr. ISTOOK. Thank you. I appreciate that.

I'm trying to make sure I cover the Chairman's priorities in his absence, and certainly there will be other things for the record.

Dr. KIRSCHSTEIN. Certainly.

RADIOACTIVE CONTAMINATION

Mr. ISTOOK. There were recent press reports regarding a young researcher who received radioactive contamination, evidently a substance in her food that appears, from press reports anyway, to have been intentional. Can you tell us, where does that investigation stand?

Dr. KIRSCHSTEIN. The investigation is ongoing by many people. Dr. Michael Gottesman, Director of the Office of Intramural Research, has the most information, I think.

Mr. ISTOOK. Okay, thank you.

Dr. GOTTESMAN. Mr. Istook, there are several ongoing investigations. The FBI is continuing their investigation to determine the cause of the contamination. The Office of the Inspector General in the Department of Health and Human Services has an ongoing investigation. And our radiation safety program, together with the Nuclear Regulatory Commission, is investigating.

There was an initial investigation by Mr. Shay's committee, which has concluded that the NIH could not be held responsible for what appears to be a deliberate contamination.

Mr. ISTOOK. What was the origin of the substance? Was it from some place at NIH? I realize NIH would not intentionally do it. But as best you can tell, did the substance itself come from some place within NIH?

Dr. GOTTESMAN. To my knowledge, none of the investigations has determined the source of the radioactive material.

Mr. ISTOOK. Okay. So it's indeterminate, maybe so, maybe not.

Dr. VARMUS. It is an isotope that's used on our campus, and on every campus. It is very commonly used.

Mr. ISTOOK. Right.

Mr. ISTOOK. What, realizing that you don't know that it came from that, nevertheless what have you done to check on enforcement of existing safeguards and evaluation to make sure that those are sufficient?

Dr. GOTTESMAN. There have been dramatic changes in the radiation safety program at the NIH in response to this incident, most related to the security of radioisotopes. There are requirements now that all radioactive materials be locked up, either under obser-

vation or under lock and key at the NIH at all times. And those have been very stringently enforced by our radiation safety program.

Mr. ISTOOK. How about the inventory? Are all substances accounted for in your inventory and have they been for, again, I'm sure you checked back for some period of time.

Dr. GOTTESMAN. The investigation, of course, looked very carefully. There were no unaccounted—for radioactive materials. The amount involved was not large compared to the amount in use in laboratories. And it's possible that some could have been used for this purpose, although as I said, we don't know the origin of the radioisotope.

There is a very extensive inventory system in place at the NIH, which involves radioisotopes being checked in centrally, so that our radiation safety program knows the origin of all radioisotopes. Those are then distributed to the labs, and each laboratory is responsible for keeping records of use and disposal of radioisotopes.

REINVENTION STRATEGIES FOR GRANT AWARDS

Mr. ISTOOK. Okay, thank you.

A final thing I wanted to cover from this, your Office of Extramural Research has been working on what they call reinvention strategies for the grant award process. Some of that of course includes electronic submission and other alternative means, seeking to save the time and the cost, and boy, you've got your batter on deck, I see. [Laughter.]

Would you describe that for us, please?

Dr. KIRSCHSTEIN. Dr. Wendy Baldwin, who is the Director of the Office of Extramural Research, will tell you about it.

Dr. BALDWIN. We're very pleased with this program, because we've had very wide participation all across the NIH in it. It's important when we look at the electronic features, which are really very appealing, to remember, that we have to re-engineer the underlying process before we move something to an electronic stage. Last year we moved full scale to streamline a lot of our review activities. And we have found that we can do that and we can retain the quality of the review. We can also save time at the review meetings. But we've been very pleased with the activities that we've taken full scale.

We also have moved to look at what we can do around our non-competing applications. Most of our work focuses on the continuing grants that go on from year to year. That's where we have ongoing contact with grantees. We've looked at where we had some redundant reporting, and we were able to reduce some of the reporting. And now that we've moved to thinking through whether we're getting exactly the right information from our grantees, we're ready to move that to an electronic format. And I think that's going to be, the next roll-out of our electronic activities.

We've looked at "just-in-time" concepts. Because we've determined that we're collecting some information too early in the process, and sometimes we don't need it. And any time we ask for information, that in fact is a burden on our investigators and on their institutions. So we have now taken a number of opportunities to pilot ways of reducing the amount of information that we ask for.

I would caution you that this is something that's very appealing and is going to have a big benefit for us. We have to be careful that we don't move sort of indiscriminately in that. One of the areas that I think we have a real potential to improve is in the human subjects review, because that's very costly on the institution side.

On the other hand, we don't want to make the review for the protection of human subjects come so close to the funding decision that it creates any undue pressure on those institutional review boards. Also in some cases institutions will have to review applications because they are being submitted somewhere else for funding.

So we're trying to be very careful in this, so that when we make a change we can be really sure it's going to have a beneficial effect for us and for the investigators and their institutions.

We have made greatly increased use of the World Wide Web. I hope you visit our home page. It saved us during the blizzard and during the furlough when we had no way to communicate the tremendous changes that we had to undergo. We had to reschedule over 50 review meetings. We had tens of thousands of investigators who wanted to know what was happening to their applications, whether groups were going to meet, and what was going to happen. And basically, that was the only way we had to communicate with them.

We have institutes now that are taking advantage of controlled access on the Web to use it to communicate with their council members. So instead of printing big council books that include all of the information they need for the council, they're able to do that on-line and dramatically reduce the amount of printing and the cost. So it's moving ahead.

Mr. ISTOOK. I've not visited your home page, what is it?

Dr. BALDWIN. NIH.GOV, the grants and contracts button.

ELECTRONIC SUBMISSION

Mr. ISTOOK. All right. When you mentioned electronic submissions and so forth, somebody could fax something that ends up with a paper copy, that's an electronic submission, they could do it in a way in which it's graphically received in your computer and thereby accessible as a graphic document, or they could do it where the data is sent to come into a data base format, where you have the ability not only to review the document, but actually to analyze and cross reference the information from different ones.

When you're talking about electronic submissions, it might be one of those, or it might be something else. Can you just tell me what you mean by electronic submissions in this case, in the application?

Dr. BALDWIN. It's not the fax-back. We use fax-back in terms of giving some information out. But it's definitely the electronic communication.

Actually, it has two forms. And this is rather important for us. One of them is the World Wide Web based format, so that in fact, the investigator sits there and enters information. We're using this for invention reporting. Because this is a very sporadic activity and it's driven by the individual investigator. It allows them to basically pull up the form on the screen. You can observe this, you can

see this through the informational side on the home page. And then we get that information electronically.

Mr. ISTOOK. Does that come in where you tie it into a data base format or into a document format?

Dr. BALDWIN. Absolutely. But we're not only using that, because there's a lot of our commerce that goes on with institutions on a very large scale, and it can't really be done by an individual sitting there accessing a World-Wide-Web page. And so for that, we are working with other Federal agencies around what's called electronic data interchange, so that we will have the common standards, so that the computer at an institution can talk to our computer, as opposed to an individual pulling up a form on the screen and sending the information.

We've worked closely with institutions to make sure they are going to accept the changes that we have in mind. They are very enthusiastic about it, but they are concerned that we take both of those strategies into account where appropriate.

Mr. ISTOOK. Okay. Very good.

Thank you very much for that.

Dr. Kirschstein, Dr. Varmus, I don't have another questions I was going to pursue here. Obviously, there will be some for the record.

Mr. ISTOOK. But there may be something which any of you wish to elaborate upon before we conclude.

Dr. VARMUS. Not for me, Mr. Istook.

Mr. ISTOOK. You're anxious to get out of here.

Dr. VARMUS. It's been a long week. [Laughter.]

Mr. ISTOOK. I very much appreciate your coming, and all the people with you.

We will then recess until 9:00 a.m. tomorrow morning.

[The following questions were submitted to be answered for the record:]

WOMEN'S HEALTH INITIATIVE

Mr. Porter: Your testimony indicates that the total cost for the Women's Health Initiative will be \$628 million. Your budget request for the past year or two has been constant at \$57 million. Within the total of \$628 million, will the annual cost of the trial vary year to year?

Dr. Kirschstein: The annual cost of the Women's Health Initiative has varied and will vary from year-to-year in response to changing cost requirements of the study. For example, the first year of funding was at \$22.9 million and supported the initial planning and the funding of the coordinating center. In the following year, funding increased to \$42.9 million as the first 16 clinical centers were funded and began recruitment for the clinical trial and observational study. The current funding level of \$57 million reflects the current status of the project. Recruitment, the most expensive activity, is being conducted by 40 clinical centers with coordination of data collection by the coordinating center. Additionally, the community prevention study, a collaborative effort with the Centers for Disease Control and Prevention (CDC) began last year. After completion of recruitment for the clinical trial and observational study in three years, adherence to treatment, follow-up and outcomes assessment will occur. These are less costly activities and the anticipated costs (and budget requests) will decline. The total cost projection is still \$628 million. A careful budget for the entire course of the project was constructed before initiation. The project is funded by contract and the year-by-year budget requests take these contractual commitments into account. Administrative costs are included in the budget estimates.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

Mr. Porter: You revised the guidelines for the inclusion of women and minorities in all NIH-supported clinical research as of June 1994. Have institutions been able to adapt to the new requirements, or have they reported problems in recruiting adequate numbers?

Dr. Kirschstein: In 1994, NIH revised its policy and published Guidelines on inclusion to meet the mandate of the NIH Revitalization Act of 1993 (PL 103-43) that women and minorities be included in all of its clinical research studies. Our experience in implementing the 1994 Guidelines has been that compliance is generally high and that many of the concerns of the scientific research community have been addressed.

Initial Review Groups focus on scientific considerations when determining whether appropriate numbers of women and minorities have been included in a study. Projects that do not meet the standard are properly identified, and administrative procedures allow for timely resolution of problems. Data collected during the first year of implementation showed that more than 92% of approximately 16,000 grant applications involving human subjects met the inclusion

requirements as submitted. When an application does not meet the inclusion requirement, NIH administrative procedures allow program staff the flexibility to work with an applicant and resolve problems in a timely manner so that, for projects which are otherwise highly meritorious, awards are not delayed because of the inclusion policy.

A number of outreach activities have been initiated by NIH to provide policy guidance and to address concerns of the scientific research community. Most recently, in February, 1996, the Office of Research on Women's Health (ORWH) reconvened a group of Institutional Review Board (IRB) Chairs from around the country along with representative members of the ORWH Recruitment and Retention Task Force, representative of NIH intramural IRBs, and other experts to share their experiences and identify concerns relating to implementation of the 1994 Guidelines.

We learned from this workshop that many of the fears previously expressed about the potential impact of the Guidelines had not materialized and that, to varying degrees, IRBs have generally incorporated the Guidelines into their review procedures. IRB representatives and other workshop participants noted the value of ongoing outreach activities by NIH to explain the new requirements to the research community and concurred with NIH's approach of focusing on scientific considerations in implementing the Guidelines. They recognized the importance of working with communities, in terms of enhancing sensitivity to community needs and research interests, fostering outreach activities and expanding representation of community members, women, and minorities on IRBs. They indicated that collaborative efforts and enhanced recruiting procedures are underway, so that recruitment of adequate numbers of women and minorities will not be an obstacle to conducting clinical research.

OFFICE OF ALTERNATIVE MEDICINE

Mr. Porter: The Office of Alternative Medicine is supporting 10 research centers. Are these centers in the traditional sense - is the field well-developed enough to support centers?

Dr. Kirschstein: The 10 Centers funded by the Office of Alternative Medicine (OAM) are not Centers in the traditional sense. While they are funded to mainstream majority institutions for the most part, they are funded towards specific disease entities, such as women's health, pain, AIDs, addiction, cancer, etc. Moreover, these Centers are primarily targeted to provide the research infrastructure for the Complementary and Alternative Medicine (CAM) community in order to begin the process of doing CAM research in a rigorous manner. These Centers use the cooperative agreement mechanism where by the OAM has substantial input into their development. These Centers were set up to develop 1) research agendas in various areas of CAM singular to their disease entities; 2) to provide technical assistance which may involve "field investigations" to alternative medical practices; 3) to perform collaborative research with investigators in CAM; and 4) to provide research reporting back to the OAM.

The intent of these Centers is to set the beginning of a system of research network for CAM practitioners or researchers in order that there will be a uniformed research approach. Additionally, these Centers provide the basis of a network across the country to investigate alternative medical practices put forth by a variety of CAM practitioners. While they are free to do original research in CAM in the traditional sense of a center, they are encouraged more specifically to do collaborative research with CAM practitioners or investigators who usually do not have the expertise or knowledge of proper research methodology.

REINVENTION EFFORTS

Mr. Porter: Central services functions at NIH seem ripe for "reinventions" with 4,450 FTEs providing direct services on campus. Have you pursued any reinvention options, such as contracting out some of the maintenance or security functions?

Dr. Kirschstein: It is important to note that of the 4,450 FTEs in the central services functions, 1,890 are associated with the NIH Clinical Center. Listed below are examples of reinvention activities sponsored by four central services divisions:

The Division of Research Grants (DRG) has streamlined by regrouping 85 separate and diverse standing study sections into 18 pilot independent Initial Review Groups. In addition, the DRG's Referral Office has made many time-consuming functions electronically available to ICD staff. Furthermore, the DRG has been designated as a service center under the area of computer network support. As a service center, the DRG supports the review branches of six other ICDs.

The Division of Computer Research and Technology (DCRT) has also undergone streamlining efforts by consolidating computer networking development and service and support activities into one functional group. In addition, the DCRT has continued to consolidate more than a dozen individual customer support operations into a single, coordinated, help desk which has improved service to its customers. In an effort to provide a single source for NIH-wide information, the DCRT is currently providing support and guidance to the NIH Data Warehouse Committee.

The Office of Research Services (ORS) has evaluated and approved a proposal to contract out mail services in order to reduce FTEs with no loss in service efficiencies. The ORS continues to seek other reinvention opportunities and is reviewing other potential service activities that could be contracted out. The ORS has also established an ORS Workforce Planning Task Team to pursue a variety of workforce planning alternatives.

Recently, the Clinical Center was reviewed by an Options Team created by the Secretary of the Department of Health and Human Services and chaired by Dr. Helen Smits, Deputy Administrator, Health Care Financing Administration. The

Options Team made four primary recommendations to improve efficiency and ensure that the Clinical Center flourishes into the next decade. First, a clear and logical governance structure including a Board of Governors comprising non-Federal and NIH representatives should be established. Second, the Clinical Center should have a clearly defined and stable budget. Third, the Board of Governors should direct development of a strategic plan with clear and measurable objectives that can serve as a keystone by which managers can allocate and distribute resources. Fourth, the Team reviewed many options for organizational structures that could increase flexibility to ensure efficiency. The Team rejected options involving full privatization of the Clinical Center or complete contracting out as well as the status quo. In response to the need for greater flexibility and responsiveness to future research needs, the Options Team and external consultants focused on designating the Clinical Center as a "Reinvention Laboratory." As a Reinvention Laboratory it could serve as a Federal demonstration site in which improved personnel and procurement practices are combined.

LABORATORY FOR DIAGNOSTIC RADIOLOGY RESEARCH

Mr. Porter: Does it make sense to locate the lab for diagnostic radiology research in the Office of the Director rather than at the Clinical Center as a shared resource whose cost is distributed among its users?

Dr. Kirschstein: While the Laboratory of Diagnostic Radiology Research (LDRR) has its own budget, transfer of LDRR to the Clinical Center, as the research arm of the Department of Diagnostic Radiology, would give LDRR a presence within a Department which shares its common scientific interests, more flexibility in recruitment and training of personnel, and the possibility of access to additional resources determined by the new Chair, Department of Radiology and the Director, Clinical Center.

We are in the process of preparing an agreement between the Deputy Director for Intramural Research and the Director, Clinical Center which describes the conditions under which LDRR will be transferred to the Department of Radiology in the Clinical Center. We expect that this transfer will probably be effected after the appointment of a new Chair of the Department of Radiology, Clinical Center.

SCIENCE EDUCATION

Mr. Porter: You have an Office of Science Education within the Office of the Director funded at a very modest (\$1.8M). Individual Institutes also have science education programs. What is the total NIH level of effort in this area?

Dr. Kirschstein: The attached table displays the total NIH level of effort for science education programs by Institute.

NATIONAL INSTITUTES OF HEALTH
Mathematics and Science Education

(DOLLARS IN THOUSANDS)

ICD	FY 1995 <u>Actuals</u>	FY 1996 <u>Appropriation</u>	FY 1997 <u>Estimate</u>
NCI	\$100,479	\$104,153	\$105,491
NHLBI	92,462	99,215	103,280
NIDR	23,139	24,113	24,575
NIDDK	54,991	56,640	57,926
NINDS	36,360	37,864	40,239
NIAID	28,841	30,635	31,295
NIGMS	108,839	112,245	113,452
NICHHD	34,827	36,123	36,430
NEI	15,100	16,241	17,241
NIEHS	23,031	23,320	24,003
NIA	34,896	35,675	35,607
NIAMS	8,567	9,132	9,330
NIDCD	11,774	13,135	13,800
NIMH	50,946	52,819	52,985
NIDA	19,527	22,514	24,198
NIAAA	12,904	14,152	14,369
NINR	4,377	4,860	4,950
NCRR	15,708	21,618	19,909
NCHGR	8,077	8,994	9,053
FIC	50	50	50
NLM	5,153	4,594	4,689
OD	<u>22,096</u>	<u>21,331</u>	<u>20,064</u>
 TOTAL	 712,144	 749,423	 762,936

Mr. Porter: What do the NIH programs bring to the science education effort that is not provided by the larger programs sponsored by the National Science Foundation?

Dr. Kirschstein: The communication of new scientific and health information gained from medical research is absolutely essential to NIH's efforts to extend

healthy life and reduce the burdens of illness and disability. In order to provide a strong return on the public's investment in NIH, we must help ensure that our research findings are understood, and implemented by the American public. One route to this goal is improved science education in the Nation's schools. NSF shares this vision and supports science education broadly, from physics to biology. It does not, however, focus on medicine and health. The NIH's well-designed science education program, as described below, contributes to, and complements the NSF's efforts by strengthening public understanding of the research and scientific process that underlay health advances.

The NIH uses its science education dollars to provide leadership and develop model programs for improving the health-related scientific literacy of the general public as well as science education for the Nation's children. To achieve this, NIH capitalizes on its greatest resource, its scientists, who are themselves parents, teachers, and students and are committed to improving science education. Some innovative programs and concepts are tested in NIH's natural laboratory, the communities in the Washington-Metro area, and utilize intramural NIH scientists. For example, the NIH Mini-Med School brings together members of the public and NIH scientists to discuss the basics of medicine and research. This pilot program has been very successful, has been presented on Capital Hill. The Speaker's Bureau is a group of scientists who volunteer to speak on medical research to schools and community groups, a program that can readily be implemented across the Nation. The NIH Internship Program brings students and teachers from across the country to NIH laboratories for summer-long research experiences.

Other model programs are being developed in the extramural community. One goal is to convey the message that science is not a collection of facts, but a dynamic process that involves the 3 C's - critical thinking, communications skills, and creativity. Examples of such NIH science education programs are listed below:

- The Science Education Partnership Awards (SEPA) grant program of the National Center for Research Resources in which working scientists and educators in enhancing precollege science education and public understanding of science across the nation and support the production and dissemination of materials for use in various educational settings.
- Minority High School Student Research Apprenticeship program, in which scientists work with minority teachers, and teachers of minority students to sharpen their scientific knowledge and technical skills and enable the teachers to transfer this knowledge into the classroom.

- The National Institute on Drug Abuse (NIDA) has developed literature for school children, explaining the effect of drugs of abuse on the human brain.
- The National Institute of Mental Health (NIMH) sponsors Challenges of the Mind, a four-part science education initiative designed to promote partnerships between scientists and K-12 students and educators.
- The National Eye Institute's (NEI) "VISION" is a curriculum produced for grades 4-8 and is being nationally distributed to vision researchers, eye care professionals, and educators.
- The NIH/Howard Hughes Medical Institute (HHMI)/Montgomery County Public Schools (MCPS) Student and Teacher Internship Program includes an intensive two-week molecular biology course and six implementation workshops for teachers.
- The Science Alliance Program establishes partnerships between scientists at NIH and elementary school educators. In 1996, NIH scientists and practicing teachers will work together to develop hands-on enrichment units which will be used by NIH scientists in classrooms and other engagements around the Metro area.
- The Snapshots of Science Web Site will open in the May, 1996 on the World Wide Web. This site is designed to attract high school students and teachers who wish to learn about the process and progress of biomedical research. The site will have a special focus on science education activities that encourage young women and other individuals traditionally underrepresented in the sciences to pursue careers in the life sciences.
- The National Institute of Environmental Health Sciences (NIEHS), the National Institute of Allergy and Infectious Diseases (NIAID), and other federal agencies sponsor the Minority On-Line Information System (MOLIS), a free source of information about the research and educational capabilities of Historically Black Colleges and Universities and Hispanic-Serving Institutions. MOLIS is also a source of federal education and research opportunities for the minority higher education community.
- The Medicine for the Public is a fall lecture series designed to help the general public understand the latest developments in medicine -- new therapies, diagnostic procedures and research. The series also provides videotapes, booklets, and fact sheets on the topics covered in the lectures.

RECRUITMENT AND RETENTION OF MINORITY WOMEN

Mr. Stokes: What are some of the current activities underway to enhance the recruitment and retention of minority women in clinical research studies?

Dr. Kirschstein: The Office of Research on Women's Health (ORWH) has provided leadership and support through several mechanisms directed toward enhancing the recruitment of women in clinical studies. In an effort to clarify issues and to help investigators recruit and retain diverse populations for their clinical studies, the ORWH established a Task Force to examine barriers to the inclusion of women in clinical trials, and then sponsored a workshop. The report of that meeting, called Recruitment and Retention of Women in Clinical Studies, notes that, "There are multiple barriers to recruiting and retaining poor women of color in clinical studies. The barriers are economic, cultural, social and psychological". Additional descriptions focus on barriers to inclusion, such as mistrust of researchers, barriers to diversity of women in clinical research, such as fear of experimentation and cultural barriers, such as different cultural beliefs. This report provides recommendations to overcome barriers to inclusion, including: cultural diversity of staff, culturally sensitive/bilingual outreach workers, and minorities and women on the research team. These barriers are now being addressed throughout the scientific and advocacy communities as minority women are being included in the design of clinical research.

While meeting the NIH requirements for recruitment and retention of women and minorities is important, scientists and their staffs, institutional review boards, NIH internal review groups, and advisory groups must assure that study participants are protected from undue coercion and from harm. NIH prepared an Outreach Notebook on the Inclusion of Women and Minorities as Subjects in Clinical Research, which contains practical guidance and a list of resources for investigators as they seek to comply with the NIH inclusion guidelines. ORWH also distributes a book of Questions and Answers to help investigators better understand the NIH inclusion guidelines.

The office has provided funding to support ongoing research to enhance the recruitment and retention of women in clinical research, particularly women of African-American, Hispanic, Native American and Asian-American/ Pacific Islander origin. ORWH also supports conferences and workshops on the health of minority women and stresses the participation of minority women as research participants and scientists at these meetings. Workshops and meetings such as the Hispanic Cancer Control Network meeting and the Surgeon General's Hispanic Latino Initiative have supported the identification of Hispanic researchers and increased the number of Hispanic investigators involved in cancer prevention and control studies. We also support African American, Asian Pacific Islanders, Native Americans and other minorities as part of the scientific team involved in conducting studies. Through these efforts, many investigators are successfully including women from diverse

groups. ORWH and other NIH representatives have made, and will be making, many presentations for outreach to the minority community and to minority physicians to increase information and opportunities for minority women's participation in clinical research.

ADDRESSING MINORITY WOMEN'S HEALTH ISSUES

Mr. Stokes: Update the committee on how minority women's health issues are being addressed through women's health programs at NIH, and through the office's collaborative efforts with the Institutes of the NIH?

Dr. Kirschstein: ORWH collaborates with respective NIH Institutes and Centers (Ics) to address gaps in knowledge and to promote areas of research on diseases and conditions that adversely affect the health of minority women. Research into conditions that are either unique to or more prevalent in subgroups of minority women are being supported and expanded, including studies of autoimmune diseases such as systemic lupus erythematosus and non-insulin dependent diabetes mellitus; obesity; cardiovascular diseases; HIV/AIDS; hypertension and cancers such as breast and cervical cancer. ORWH administrative supplements to grants expanded biomedical and behavioral research to include greater numbers of minority women in such investigations as studies of smoking habits in Asian women, the implications of cervical dysplasia in various racial/ethnic subgroups and research on skeletal homeostasis in black and white populations with a particular emphasis on determining biomarkers for bone disease. The "Study of Women at Menopause," an ongoing collaborative study to define this transition period in the lives of women, with the National Institute of Aging and the National Institute of Nursing Research, is specifically designed to include the participation of diverse racial/ethnic subpopulations at each performance site so that the results obtained will have greater relevance and will expand the scope of scientific knowledge regarding menopausal changes in women from different cultural and lifestyle experiences. In addition, workshops, symposia, and conferences have also been cosponsored in which research issues pertinent to the health of women, particularly minority women, have been discussed. For example in the ORWH Seminar Series, strong efforts are made to include minority speakers in all proceedings. This opportunity provides guests with an opportunity to present their research, focus on health issues as they may unequally affect minority populations, and to network with NIH scientists. These and other forums have increased awareness of the effects of specific diseases and conditions on minority women.

Because representation of women and minorities is now required to participate in NIH-supported clinical research, even more minority women are being recruited into clinical trials, such that future results should provide greater scientific information about not only gender, but ethnic/racial factor in disease and health.

Further, the Women's Health Initiative, the largest U.S. study ever undertaken related to prevention of disease in post menopausal women, has three major components: a randomized controlled clinical trial of promising but unproven approaches; an observational study to identify predictors of disease; and a study of community approaches to developing healthful behaviors. The study has been designed also to address potential ethnic/racial differences among women for cardiovascular disease, cancer and osteoporosis, and will include significant numbers of minority women among its participants. Currently, accrual of minority women is on target at approximately 20% of the sample.

INCLUSION OF MINORITY WOMEN IN CLINICAL RESEARCH

Mr. Stokes: What is NIH doing to monitor the inclusion of minority women in clinical research?

Dr. Kirschstein: In 1994, NIH revised its policy and published Guidelines on inclusion to meet the mandate of the NIH Revitalization Act of 1993 (PL 103-43) that women and minorities must be included in all of its clinical research studies. The ORWH, in conjunction with the Office of Research on Minority Health (ORMH), the Office of Extramural Research, and the Office of Intramural Research, has made considerable progress in implementing the 1994 Guidelines.

In addition, ORWH has taken the lead in establishing and implementing a computerized tracking system to monitor demographic data on subjects enrolled in both extramural and intramural human subject studies. All investigators are required to report enrollment data by gender and racial/ethnic group. Baseline data have been compiled on an NIH-wide basis for FY 1994 awards. Preliminary analysis of data for NIH intramural studies conducted at the Warren G. Magnuson Clinical Center and NIH extramural studies conducted throughout the country indicated that substantial numbers of women and minorities have been included as research subjects. Data collection will be ongoing to allow for examination of trends in the future.

Our policy and procedures are now in place and are working. Review procedures now emphasize that inclusion is considered an issue of scientific merit in determining funding decisions. Extensive training has been conducted to familiarize NIH staff with the new requirements, and numerous outreach activities have been undertaken to continue dialog on this issue with the scientific research community.

Mr. Stokes: What actions have been taken to increase outreach, especially into the community, to enhance the participation of minority women in clinical research?

Dr. Kirschstein: In 1994, NIH revised its policy and published Guidelines on inclusion to meet the mandate of the NIH Revitalization Act of 1993 (PL 103-43) that women and minorities be included in all of its clinical research studies. The

Revitalization Act also requires NIH to conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in projects of clinical research. In addition to describing the proposed study population, applicants for NIH grants and contracts must also describe their efforts to recruit and retain women and minorities as participants in research studies. If these plans are judged as unacceptable, it will be considered a scientific weakness in the study design and will be reflected in the priority score assigned to the application.

The ORWH has provided leadership and support of outreach activities through several mechanisms directed toward enhancing the recruitment of women in clinical studies. In an effort to clarify issues and to help investigators recruit and retain diverse populations in their clinical studies, the ORWH established a Task Force to examine barriers to the inclusion of women in clinical trials, and then sponsored a workshop. The report of that meeting, called Recruitment and Retention of Women in Clinical Studies, provides recommendations to overcome barriers to inclusion, including: cultural diversity of staff, culturally sensitive/bilingual outreach workers, and minorities and women on the research team. These barriers are now being addressed throughout the scientific and advocacy communities as minority women are being included in the design and conduct of clinical research.

Recently, in February, 1996, ORWH reconvened a group of Institutional Review Board (IRB) Chairs from around the country, along with representative members of the ORWH Recruitment and Retention Task Force, representatives of NIH intramural IRBs, and other experts to share their experiences and identify concerns relating to implementation of the 1994 Guidelines. IRB representatives and other workshop participants noted the value of ongoing outreach activities by NIH to explain the new requirements to the research community and concurred with NIH's approach of focusing on scientific considerations in implementing the Guidelines. The workshop participants indicated that collaborative efforts and enhanced recruiting procedures are underway, so that recruitment of adequate numbers of women and minorities will not be an obstacle to conducting clinical research.

ACHIEVEMENTS IN SCIENCE

Mr. Stokes: What progress has been made, and what initiatives have been planned to increase the number of women, especially minority women, and their achievements in science?

Dr. Kirschstein: The ORWH has made great strides to increase the number of women, especially minority women, and their achievements in science. The ORWH sponsored a public hearing and a workshop in 1992. The barriers and recommendations are highlighted in a report, "Women in Biomedical Careers: Dynamics of Change-Strategies for the 21st Century", available through ORWH. Barriers include: recruiting women to biomedical career; family responsibilities; sex

discrimination and sexual harassment; research initiatives on women's health; gender sensitivity; and special concerns of minority women in science.

- The Reentry into the Biomedical Sciences Program was developed as a pilot program in 1992 to help fully trained scientists (women and men) reestablish careers in biomedical or behavioral science after taking time off to care for children or parents or to attend to other family responsibilities. An intramural component was also implemented. The success of the pilot program resulted in its expansion to a trans-NIH program supported by 17 ICs. To date 31 awards have been made. A workshop was held to bring together awardees and mentors to evaluate: (1) the effectiveness of the ORWH reentry program, and (2) the role and the effectiveness of the mentoring component.
- A program, Target Women was developed in conjunction with the NIH Office of Science Education to overcome barriers to the advancement of women. An ORWH/OSE Speakers Bureau has been set up to increase the visibility of a diverse group of women scientists; a "Writing about Science" course to teach young scientists to write about science effectively including approximately 30% female and male minority participants; a "Talking about Science" course to teach young scientists how to present scientific data effectively including about 30% minority participants; a "Women in Science" Poster Series which will feature prominent women scientists including minority women; a Young Women's Network Brown Bag Series for summer interns; and the Career Development Workshops area designed to support the successful career development of young post doctoral intramural researchers.
- ORWH supports programs which specifically target minorities in science such as, the Science Enrichment Program to encourage high school students from underrepresented minorities and underserved groups to pursue careers in science, a Research Career Program (K award) which has funded a Hispanic new academic investigator for research on "Drug Abuse Prevention in Hispanic Women", the Science Enrichment Partnership Award (SEPA) to encourage active biomedical/behavioral scientists by providing comprehensive training in science and mathematics, and the Hispanic Youth Initiative, which is designed to motivate, prepare, and encourage Hispanic high school students to pursue a career in the health sciences.

MINORITIES IN CLINICAL RESEARCH

Mr. Stokes: What are some of the current activities underway to enhance the recruitment and retention of minorities in clinical research studies?

Dr. Kirschstein: There are a number of such projects. A collaborative effort is underway between the faculties of Meharry Medical College and Vanderbilt University School of Medicine to explore the lack of minority participation in the AIDS clinical trials. The minority AIDS Clinical Trials Unit (ACTU) in Nashville, Tennessee is developing techniques for improving recruitment, retention, and compliance of minorities, women and drug abusing AIDS patients.

- At Yale University, one component of the AIDS Clinical Trial Unit is developing a psychological profile of clinical trial participants which is related to knowledge, attitudes and behavior associated with recruitment, adherence and retention in clinical trials. The long-term objective is to improve recruitment, adherence and retention in clinical trials particularly among hard-to-reach populations of women, minorities and intravenous drug users.
- The African American Breast Cancer Human Genome Study at New York Medical College is piloting an innovative project that links studies regarding the genetics of cancer susceptibility, by establishing a unique lymphocyte/DNA repository of African American women with breast cancer, and with the interventions designed to increase the participation of African Americans into breast cancer clinical trials.

OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: Update the Committee on how minority health issues are being addressed through the Office of Research on Minority Health and through the office collaborative efforts with the Institutes, Centers and Divisions of the NIH.

Dr. Kirschstein: The ORMH at the NIH seeks information on minority health issues through regional and national meetings at which those interested in specific minority group health issues may inform the ORMH of special needs. ORMH also frequently reviews the statistical data produced by the Centers for Disease Control and Prevention and other federal agencies. These data show the relative importance of various health issues related to specific American racial and ethnic groups. One of the best resources is the major collaboration of ORMH with the NIH Institutes, Centers and Divisions (ICDs), to identify and attack health problems which affect our nation's minority citizens in a disproportionate manner. Once identified, the ORMH can provide additional funding to the ICDs to initiate new research

programs which will rapidly begin the search for an answer to the particular health problem creating the greater suffering and shorter lifespan of our minority citizens.

INCLUSION OF MINORITIES IN CLINICAL RESEARCH

Mr. Stokes: What is NIH doing to monitor the inclusion of minorities in clinical research?

Dr. Kirschstein: Adherence to the NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research is monitored during the development, review, award and conduct of research by NIH health scientist administrators. NIH funding components will not award any grant, cooperative agreement or contract or support any intramural project which does not comply with the guidelines. Studies that do not meet the standard are identified, and administrative procedures put in place to allow for timely resolution of the problems. Awardees are required to report annually on the enrollment of women and men, and on the race and ethnicity of research participants. For the first time, NIH is now able to track demographic data for study populations on an NIH-wide basis. A preliminary analysis of the first available year of NIH-wide enrollment data shows that substantial numbers of both women and minorities have been included as research subjects. Data compiled in future years will allow for longitudinal examination of trends and continued monitoring of compliance.

OUTREACH ACTIVITIES

Mr. Stokes: What actions have been taken to increase outreach, especially into the community, to enhance the participation of minorities in clinical research?

Dr. Kirschstein: The following are examples of community outreach projects designed to enhance the participation of minorities in clinical research:

- At Johns Hopkins University, a nutrition education study utilizes a community-based approach to an urban African American community. The overall goal is to achieve a significant increase in the proportion of African Americans consuming a low fat, low salt "prudent" diet and to increase the number who have optimal levels of blood pressure and total blood cholesterol. Community focus groups will be conducted to design culturally-specific nutrition education modules to be used in two subsequent randomized trials.
- At the Emory University Alzheimer's Disease Center, the Education and Information Transfer Core is establishing a minority outreach program to recruit patients and families for all aspects of diagnosis, care management, family support, and scientific research.

MINORITY ACHIEVEMENTS IN SCIENCE

Mr. Stokes: What progress has been made and what initiatives have been planned to increase the number of minorities, especially disadvantaged minorities and their achievements in science?

Dr. Kirschstein: The NIH has had in place, for many years, two primary undergraduate research training programs well known in the scientific community, both sponsored by the National Institute of General Medical Sciences. These are the Minority Access to Research Careers (MARC) and Minority Biomedical Research Support (MBRS) programs. They have both encouraged and supported many minority students to obtain the Ph.D. and enter biomedical research careers. The numbers of minorities obtaining Ph.D.s in the life sciences has steadily increased over the years in spite of the many other, potentially more lucrative, career options available to young people. New programs sponsored by ORMH, provide additional resources for students. One such program is "Bridges to the Future", which encourages students in two year colleges to continue for the bachelor's degrees at partner colleges, and students in terminal Master's degree institutions to continue work on the Ph.D. degree at a partner University. Another new ORMH sponsored program is the Minority International Research Training Program (MIRT), designed to expose U.S. minority students and faculty to foreign research opportunities, which broadens their research experience, giving them a chance to be more independent, more competitive and to develop their leadership skills. At the same time the ORMH is collaborating with the National Science Foundation in creating programs which improve science and mathematics education at the kindergarten through grade 12 levels. This includes enhancing teacher training in science, improvements in educational methods and providing students with new and exciting hands-on science training. For the older pre-college students, mentored laboratory research opportunities are offered. Programs are available to provide financial support for disadvantaged minority students from high school age through their post-doctoral training, to enable them to develop an interest and enhance their skills in biomedical research.

MINORITY POPULATIONS IN CLINICAL TRIALS

Mr. Stokes: AIDS Clinical Trial Groups are critical to NIH research needs while providing much needed high quality medical care to people living with HIV disease. What is NIH doing to help ensure women and communities of color continued access to community-based HIV-related clinical trials of promising new therapies?

Dr. Kirschstein: The Office of AIDS Research (OAR) is committed to assuring that the participation of specific populations in NIH-funded clinical trials reflects the changing demographics of HIV infection and AIDS, including women, children, adolescents, minorities, drug users, the urban poor, and individuals residing in rural areas. Recruitment and enrollment of these populations is a high priority in NIH-

sponsored studies and these issues are specifically addressed in the NIH Plan for HIV-Related Research developed by the OAR. NIH has published and implemented stronger guidelines requiring the inclusion of women and minorities in all NIH-supported clinical studies, and the Office of Research on Women's Health and the Office of Research on Minority Health continue to monitor compliance with these guidelines. It must be pointed out that the NIH-supported AIDS clinical trials networks strive to ensure that a sufficient proportion of minority participants are enrolled into the clinical trials for the purpose of assuring that the results of the research may be generalizable to the affected HIV population. Efforts are ongoing to identify and overcome real or potential barriers to recruitment and retention of study participants in trials. Pediatric clinical trials enroll principally minority populations.

In addition, the ACTG supports the AIDS Clinical Trials Infrastructures in Minority Institutions to enhance HIV clinical research performed at minority institutions. Four institutions received awards: Howard University, Meharry Medical College, the University of Puerto Rico, and the University of Hawaii. This program increases the number of minority staff involved in ACTG research and the number of minority participants in the studies.

COMMUNITIES OF COLOR, WOMEN AND CHILDREN IN TRIALS

Mr. Stokes: I understand that, during FDA's recent drug approval hearings, the pharmaceutical industry was criticized for having virtually no data about the efficacy and safety of AIDS related drugs when used by communities of color, women and children living with HIV disease. Does NIH have a similar problem, explain?

Dr. Kirschstein: The NIH does not have a similar problem.

Mr. Stokes: To what extent is NIH committed to ensuring these communities access to the therapies and protocols available at the NIH?

Dr. Kirschstein: Guidelines on the Inclusion of Women and Minorities in Clinical Research were implemented that require every study to include women and minorities in study populations. Unless an investigator can clearly justify why such individuals are not included in the study, NIH funding will not be provided. Pediatric AIDS clinical trials are carried out by NIAID, NICHD and NCI. These clinical trials networks enroll primarily minority populations. The NIAID/NICHD funded collaborative Pediatric AIDS Clinical Trials Group provides flexibility to adjust the location of trials sites to accommodate the changing epidemiology of HIV in women and children.

TRAINING AND RECRUITMENT OF MINORITY RESEARCHERS

Mr. Stokes: In the U.S., HIV/AIDS continues to disproportionately impact minority communities. What progress has the NIH made to date to recruit, train, and hire researchers from communities of color; and to increase the number of extramural HIV/AIDS researchers, in extramural settings, who are doing research in communities of color are themselves people of color?

Dr. Kirschstein: NIH focuses attention on the recruitment of minority physicians, particularly African Americans, to conduct research and administer research programs. The OAR provides funding and support for the NIH AIDS Loan Repayment Program, which was authorized by Congress to encourage qualified physicians and scientists to engage in AIDS-related research at the NIH. The program strives to attract qualified minority researchers. The Loan Repayment Program Regarding Clinical Researchers from Disadvantaged Backgrounds, also authorized by Congress, has been established by NIH, based on the AIDS Loan Repayment model. This program provides loan repayment for qualified health professionals from disadvantaged backgrounds to conduct clinical research as employees of the NIH. The OAR has provided support for a series of meetings since 1989 sponsored by the Public Health Service, including the National Congress on the State of HIV/AIDS in Racial and Ethnic Communities.

Mr. Stokes: What is the NIH's plan to increase the representation of researchers from communities of color in the upcoming year, as well as over the course of the next authorization of the NIH?

Dr. Kirschstein: The OAR supported the AIDS Postdoctoral Fellows Meeting that provided minority predoctoral and postdoctoral fellows, junior faculty, and physicians in training the opportunity to interact with senior AIDS researchers. State-of-the-art information on AIDS research was discussed. The meeting served to enhance recruitment of minorities into the NIH and NIH-sponsored Institutional Training Grant programs.

OAR supports activities aimed at informing minority biomedical and behavioral health professionals about opportunities in the AIDS Loan Repayment Program and NIH research through sponsorship of exhibits and attendance at meetings such as the National Medical Association, the Student National Medical Association, the American Medical Student Association, and through outreach to the Dean of Students and Financial Aid Officers at Historically Black Colleges and Universities.

OAR COORDINATION

Mr. Stokes: Recent approval of a new class of HIV drugs (the protease inhibitors) has had a tremendous and positive impact in the HIV/AIDS communities. With regard to the NIH, what specific reauthorization

improvements and refinements are needed to strengthen the coordination, communication and working relationships between the NIH, FDA and private industry?

Dr. Kirschstein: We do not anticipate any changes in the authorizing legislation with regard to these coordinating roles of the OAR. OAR takes an active role in the relationship between NIH, the FDA, and the pharmaceutical industry. Representatives of the pharmaceutical companies have been included as participants in all OAR-sponsored planning and evaluation functions. The OAR provided support to the recently completed National AIDS Drug Task Force, which brought together government, industry, and community representatives to identify obstacles to drug development. The Vice President also recently held a meeting including senior government scientists and industry representatives to identify obstacles in vaccine development research.

Mr. Stokes: Additionally, what reauthorization refinements are needed to accomplish such between NIH, HRSA, CDC and SAMHSA?

Dr. Kirschstein: We do not anticipate any changes in the authorizing legislation in our relationship with HRSA, CDC or SAMHSA.

Mr. Stokes: What is the role and responsibility of the Office of AIDS Research in both of these cases?

Dr. Kirschstein: The NIH Revitalization Act of 1993 states that the "Director of the Office shall act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the National Institutes of Health and (A) shall serve to represent the National Institutes of Health AIDS Research Program at all relevant Executive branch task forces and committees and (B) shall maintain communications with all relevant Public Health Service agencies and with various other departments of the Federal Government, to ensure the timely transmission of information concerning advances in AIDS research and the clinical treatment of acquired immune deficiency syndrome and its related conditions, between these various agencies for dissemination to affected communities and health care providers."

IMPLEMENTATION OF EVALUATION REPORT

Mr. Stokes: The recently released external review panel report, calls for increased emphasis on the pathogenesis of HIV disease, vaccine research, and behavioral and biomedical research in HIV prevention. To what extent does the NIH plan to implement the panel's recommendations?

Dr. Kirschstein: The Director of OAR, the Director of NIH, and the Directors of the NIH Institutes and Centers have initiated a series of meetings to design an

appropriate implementation plan for these recommendations. The evaluation was carried out by non-government scientists, researchers and community representatives. The evaluation report represents their recommendations to the NIH.

Mr. Stokes: To what extent does NIH plan to involve the scientific, policy, and consumer communities in helping craft an associated implementation plan?

Dr. Kirschstein: The implementation process will be carried out as an internal NIH process in response to the report which was prepared by scientists and health policy decision-makers from across the country.

OFFICE OF RESEARCH ON WOMEN'S HEALTH

Mrs. Lowey: In your written testimony, you state that the budget request for the NIH Office of Research on Women's Health will allow it to identify "continuing gaps in knowledge about women's health". In your opinion, what are the most serious continuing gaps in our knowledge about women's health and how is NIH addressing these gaps?

Dr. Kirschstein: While much has been accomplished, there are many diseases and conditions that affect the health of women for which we do not have adequate scientific information. The NIH Office of Research on Women's Health (ORWH) continually refines and implements its research agenda and its priorities through consideration of new scientific advances and evolving new issues affecting women's health. It focuses not only on leading causes of death in women, but also on other conditions that may affect the quality of women's lives and health. Of particular importance is the underlying need for research studies on prevention of acute and chronic diseases. Many of these studies will benefit both women and men because they investigate the role of sex and gender in the prevention, pathogenesis, progress and treatment of disease and disability.

Some of the areas of research that are considered ongoing priorities because of a need for expanded scientific data include, for example, autoimmune diseases, especially as they lead to chronic diseases or life threatening illnesses. Among these diseases is systemic lupus erythematosus (lupus), where 90 percent of the patients are women. Working with the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), ORWH is co-funding the first national study on the safety of estrogen use in women with lupus. This study will provide important information about therapies that could have significant impact on the health and quality of life for patients with lupus. NIAMS and ORWH are expanding research into the basic mechanisms underlying autoimmunity (such as immune mechanisms in rheumatoid arthritis), gender differences in these processes, and their clinical applications.

Gaps in research knowledge on reproductive health continue to be addressed by NIH. For example, the NIH conference "Endometriosis 2000" highlighted deficiencies in understanding this disease. Endometriosis is still poorly defined and treatment is limited by major gaps in basic knowledge of the disease process. Studies under the request for applications (RFA) "Alternatives to Hysterectomy-- Bench to Bedside" focus on basic science that is necessary to provide a foundation for clinical approaches to benign gynecologic disease, with an emphasis on fertility-sparing treatments. In close collaboration with the National Institute of Child Health and Human Development (NICHD), ORWH continues to support research on endometriosis. In addition, sexually transmitted diseases are another area where serious knowledge gaps remain.

Other examples are: Urologic conditions which, although often considered a problem for older women, affect women across their life course. With the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), ORWH co-sponsored a RFA on Interstitial Cystitis and Other Bladder Disorders of Women". A recently funded NIDDK/ORWH RFA on "Basic and Epidemiologic Research Related To Disorders of the Urinary Bladder" supports research on normal and abnormal urinary functions in females, including incontinence that is one of the principle causes of loss of independent living in later life.

Mood disorders, eating disorders, anxiety and addictive behaviors. Although the National Institute of Mental Health (NIMH) and ORWH co-sponsor a program announcement for research on mental disorders, symptoms, and behavioral, cognitive and social concerns in women across the life span behavioral health research must identify, prevent, and treat the factors that result in such situations. ORWH has joined several other OD offices, Institutes and Centers (Ics) and other Federal agencies (Department of Justice, Centers for Disease Control and Prevention Administration on Children, Youth, and Families) in sponsoring a joint research solicitation on violence against women, an ongoing research priority.

Molecular bases for sexual and gender differences in disease are poorly understood. Areas for future research include the study of receptor populations and enzyme level differences, implications for unique pharmacokinetics and pharmacodynamics of medications in women, and the effects of hormone replacement therapy or oral contraceptives on the pharmacokinetics and pharmacodynamics of other medications.

ORWH has been at the forefront in calling attention to the need for research on risk factors for diseases in women of different racial ethnic, and socioeconomic groups and in developing disease prevention strategies targeted to women. Adequate numbers of women in research studies are required for results to give scientific validity and to be widely applicable to the entire American population. ORWH will provide research funds to expand recruitment of various subpopulations of women in NIH supported grants and to ensure that the mandates of the 1993 NIH Revitalization Act for inclusion of women and minorities in research are met.

Mrs. Lowey: Can you update us on the progress NIH is making in meeting the guidelines regarding the inclusion of women and minorities in clinical trials?

Dr. Kirschstein: In 1994, NIH revised its policy and published Guidelines on inclusion to meet the mandate of the NIH Revitalization Act of 1993 (PL 103-43) that women and minorities be included in all of its clinical research studies. The Office of Research on Women's Health (ORWH), in conjunction with the Office of Research on Minority Health, the Office of Extramural Research, and the Office of Intramural Research, has made considerable progress in implementing the 1994 Guidelines.

Our policy and procedures are now in place and are working, in part due to the fact that implementation of the policy is based on scientific considerations. Review procedures now emphasize that inclusion is considered an issue of scientific merit in determining funding decisions. Extensive training has been conducted to familiarize NIH staff with the new requirements, and numerous outreach activities have been undertaken to continue dialog on this issue with the scientific research community.

A significant accomplishment has been the development of a computerized tracking system to monitor demographic data on subjects enrolled in both extramural and intramural studies. Baseline data have been compiled on a NIH-wide basis for FY 1994 awards for which enrollment figures were reported in FY 1995. Data collection will be ongoing to allow for examination of trends in the future.

- Preliminary analysis of data for NIH extramural studies conducted throughout the country showed that substantial numbers of women and minorities have been included as research subjects. Approximately 50% of the subjects in extramural studies were women, approximately 46% men, and approximately 3% were unknown. Among minority subjects, representation in extramural studies was highest for Black (not Hispanic) subjects (23.99%) and lowest for American Indian/Alaskan native subjects (1.02%).
- Preliminary analysis of data for NIH intramural studies conducted at the Warren G. Magnuson Clinical Center also showed that substantial numbers of women and minorities have been included as research subjects. Approximately 49% of the patients seen in 1994 were women; approximately 51% were men. Among minority subjects, representation in intramural studies was highest for Black (not Hispanic) subjects (9.83%) and lowest for American Indian/Alaskan native subjects (0.24%).

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

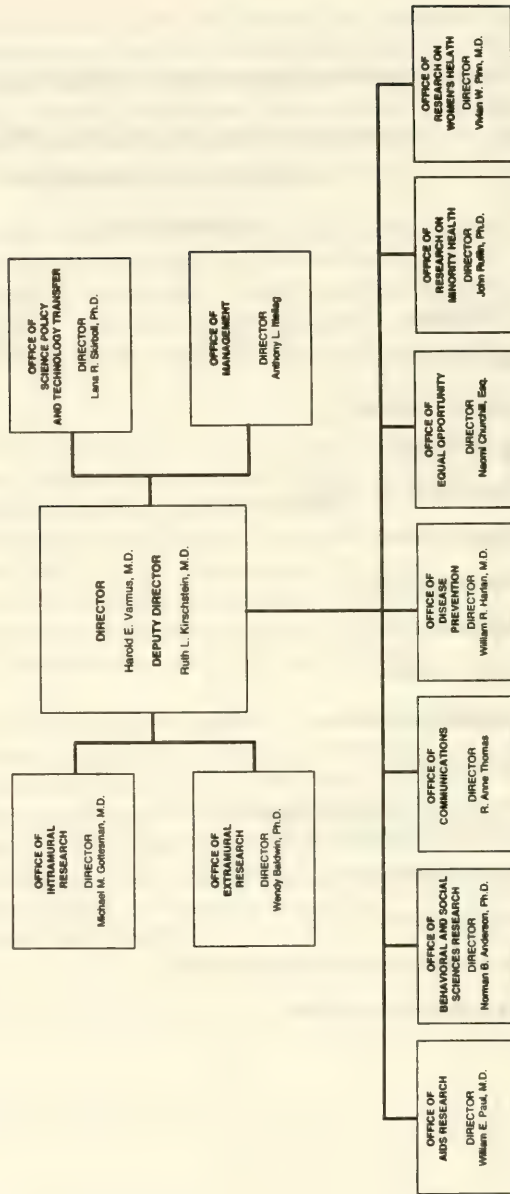
NATIONAL INSTITUTES OF HEALTH

Office of the Director

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NATIONAL INSTITUTES OF HEALTH

Office of the Director Organization Structure



NATIONAL INSTITUTES OF HEALTH

Office of the Director

For carrying out section 301 of title IV of the Public Health Service Act with respect to the Office of the Director, \$226,913,000; Provided, That funding shall be available for the purchase of not to exceed five passenger motor vehicles for replacement only: Provided further, That the Director may direct up to 1 percent of the total amount made available in this Act to all National Institutes of Health appropriations to activities the Director may so designate: Provided further, That no appropriations shall be increased or decreased by more than 1 percent by any such transfers and that the Congress is promptly notified of the transfer: Provided further, That NIH is authorized to collect third party payments for the cost of clinical services that are incurred to the National Institutes of Health research facilities and that such payments shall be credited to the National Institutes of Health Management Fund: Provided further, That all funds credited to the NIH Management Fund shall remain available for one fiscal year after the fiscal year in which they are deposited.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH**Office of the Director****Language Analysis**

Language Provision	Explanation
"Authorized to collect third party payments for the cost of clinical services"	Language has been added that will allow the NIH to collect third party payments for clinical services provided in research facilities for use in offsetting the expenses associated with the construction of the Clinical Research Center
"funds credited to the NIH Management Fund shall remain available for one fiscal year after the fiscal year in which they are deposited"	Language has been added that will permit more flexibility in the use of third party payments.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Amounts Available for Obligation 1/

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Appropriation.....	\$218,367,000	\$233,890,000	\$226,913,000
Reduction in accordance with P.L. 103-333.....	-438,000	---	---
Reduction in accordance with P.L. 104-19.....	-47,000	---	---
Subtotal, adjusted appropriation.....	217,882,000	233,890,000	226,913,000
Real transfer to: NIGMS for MARC and MBRS Programs.....	-3,375,000	---	---
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority....	-184,000	---	---
Comparative transfer to: NIDDK for Nutrition Coordinating Committee.....	-446,000	---	---
Comparative transfer to: NIDCD for two positions.....	-215,000	---	---
Comparative transfer from: ADAMHA to OD for accounting services.....	+572,000	---	---
Subtotal, adjusted budget authority.....	214,234,000	233,890,000	226,913,000
Unobligated balance, lapsing.....	-40,000	---	---
Total obligations.....	214,194,000	233,890,000	226,913,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1995 - \$55,000,000; FY 1996 - \$55,000,000; FY 1997 - \$55,000,000.

Also excludes funding for HIV activities: FY 1995--\$24,107,000; FY 1996--\$26,598,000; FY 1997--\$24,600,000, included in Office of AIDS Research, NIH.

Justification
The Office of the Director

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
749	\$214,234,000	657	\$233,890,000	657	\$226,913,000	—	-\$6,977,000
	(158,577,000)*		(177,131,000)*		(170,493,000)*		(-6,638,000)*

* Funds Reimbursed or Directly Supporting ICDs.

This document provides justification for the FY 1997 Non-AIDS activities in the Office of the Director (OD), National Institutes of Health. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The Office of the Director (OD) provides leadership, coordination, and direction in the formulation of policy related to biomedical research and research training. To carry out this role, the OD Offices centrally coordinate extramural and intramural research and science policy; technology transfer policy and protection of intellectual property; encourage research and training programs on the health of women and minorities; promote disease prevention; foster social and behavioral sciences; advance medical applications of research; further science education; coordinate public affairs and legislative activities; provide oversight for contract and grant administration, and financial and human resource management. Other NIH centralized services provided to the NIH Institutes, Centers, and Divisions (ICDs) include activities related to equal employment opportunity, acquisition of goods and services, property management, logistics, and information resource management.

Over the past five years, 72 percent of the OD's increase in appropriations for non-AIDS activities has been directed to, and oversight of, cross cutting NIH programs such as the Women's Health Initiative, the Minority Health Initiative, and alternative and complementary medicine.

While the OD provides the overall direction, coordination, and oversight to these programs, the ICDs manage the actual program operations. The FY 1997 budget request for the Office of the Director is \$226.913 million, a decrease of \$6.977 million from the FY 1996 level.

Beginning in FY 1995 and continuing in FY 1996, the OD embarked on several reorganizations with the goal of streamlining operations, reducing control and headquarters positions, and decreasing the number of supervisory personnel. Since FY 1994, the OD has eliminated more than 90 headquarters positions and efforts are continuing to reduce control positions. Other examples of streamlining activities include: the Office of Human Resource Management (OHRM) which eliminated unnecessary layering by consolidating 15 organizations to five. In addition, the OHRM achieved a 30 percent reduction in headquarters personnel while increasing its supervisory to employee ratios from 1:4 to 1:12.6. Likewise, the Office of Administration

Fiscal Year	Appropriation	Funds Reimbursed or Directly Supporting ICDs	Full-time Equivalents (FTEs)
FY 1992	\$130.465 Million	-\$85.952 Million	699
FY 1993	\$175.381 Million	-\$127.808 Million	716
FY 1994	\$202.685 Million	-\$151.586 Million	700
FY 1995	\$214.234 Million	-\$158.577 Million	749
FY 1996	\$233.890 Million	-\$177.131 Million	657
FY 1997	\$226.913 Million	-\$170.493 Million	657

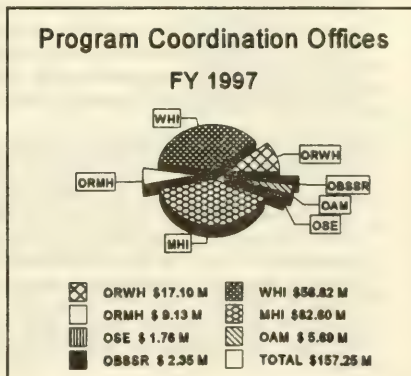
Figure 1 - OD Funding Over the Past Five Fiscal Years

was reorganized to streamline operations. Its plan resulted in delayering the organization from 12 Branches to three Divisions and four Branches. We eliminated 17 supervisory positions and increased the supervisory to employee ratios to 1:11. In FY 1997, the OD will continue to reevaluate its organizational structure to further align and streamline activities and reduce redundancy.

The OD also established several nonresearch collaborations involving Service Centers and shared resources with other ICDs and agencies. For example, the Office of the Chief Administrative Officer collaborated with the Division of Computer Research and Technology to share resources and improve the management, direction, and the infrastructure of the OD's Local Area Network Service Center. Another example is the Service Center established by the Office of Human Resource Management for several ICDs to handle the recruitment process for Senior Executive Service positions.

Program Coordination

Over the last six years, NIH has responded to focused public interest by emphasizing certain research areas that transcend the boundaries of individual NIH ICDs: women's health research; minority health research; social and behavioral sciences; and alternative medicine studies. The NIH, with support from Congress, created offices within the Office of the Director to encourage trans-NIH coordination and activities. The FY 1997 budget request for these offices is \$157.25 million for these activities.



The Office of Research on Women's Health

We established the Office of Research on Women's Health (ORWH) in September 1990 to serve as the focal point for women's health research across NIH, ensuring that research conducted and supported by NIH appropriately addresses issues regarding women's health, that women are appropriately participating in clinical research, especially clinical trials, and that efforts are directed to stimulating opportunities for women in biomedical careers. Since the NIH Revitalization Act of 1993, we have expanded the ORWH's existing responsibilities. The budget request is for \$17.103 million.

The ORWH has developed a comprehensive trans-NIH research agenda for women's health based on new and emerging scientific findings. It is a multi-disciplinary approach to the study of issues across the life span and includes, basic, clinical, behavioral, and epidemiologic research studies. During FY 1997, the ORWH will continue to co-fund, with the NIH ICDs, new initiatives and to provide supplements for existing NIH grants. We revised the NIH Guidelines for inclusion of women and minorities as subjects in clinical research for all NIH grant and contract applications, proposals, and intramural projects submitted after June 1, 1994. As a result, the ORWH, for the first time, has tracked the number of women and minorities in NIH-supported clinical trials; those data, for Fiscal Year 1994, will be available shortly. Last year, a report from the Institute of Medicine made recommendations on legal and ethical issues surrounding the inclusion of women in clinical trials. The ORWH plans to convene a meeting for Institutional Review Board chairs to address the impact of the revised inclusion requirements and recruitment/retention efforts on clinical research at their institutions.

In FY 1996 and FY 1997, the ORWH will focus on cardiovascular disease, the health of underrepresented and culturally and economically diverse populations of women, reproductive health including at-risk pregnancy, lung, breast and cervical cancers, and biobehavioral and other risk factors that impact on the health of women. Other ORWH-supported research activities will focus on genetic issues, the health effects of environmental exposures on chronic diseases in women and the molecular bases for gender differences in disease manifestations including receptor populations and enzyme level differences and their implications for unique pharmacokinetics and pharmacodynamics of medicine in women. The ORWH will pursue new collaborative efforts to eliminate remaining gaps of knowledge about the health of men and women.

The Office will continue activities to increase opportunities for women in biomedical careers by identifying obstacles to women's participation in research careers. We will develop programs, such as the reentry program, to encourage fully trained women and men to reenter an active research career after interruptions caused by family responsibilities. This initiative and other ORWH-supported collaborations are enhancing the professional opportunities for women in biomedical research. The career development agenda in FY 1996 be advanced based on a series of initiatives and recommendations from the report, *Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century*. The ORWH recently held a workshop to assess the Reentry Scientists Program. Because of this workshop, the ORWH plans to sponsor new initiatives and expand the NIH Reentry Scientists Program in FY 1997.

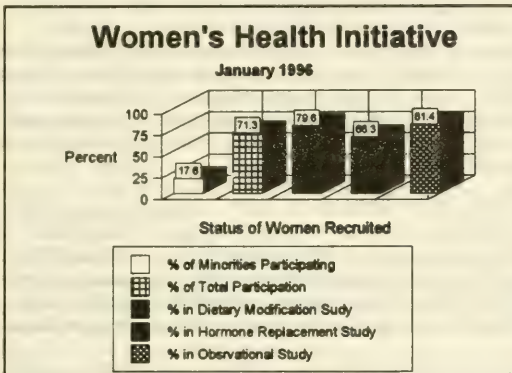
The Women's Health Initiative

Another activity centered in the NIH Office of the Director is the Women's Health Initiative (WHI), a \$628 million, 15-year project involving 164,500 women aged 50-79. This is one of the largest U.S. prevention studies of its kind. It focuses on strategies for preventing some major causes of death, disability and frailty in older women of all races and socioeconomic backgrounds: heart disease, breast and colorectal cancer and osteoporosis. Experts from across the various NIH ICDs and from outside government participated in designing the WHI. It is one of the most definitive, far-reaching clinical trials of women's health ever undertaken in the U.S.

The WHI, carried out under the direction of the Office of Disease Prevention, has three major components: a randomized controlled clinical trial of promising but unproven approaches to prevention; an observational study to identify predictors of disease; and a study of community approaches to developing healthful behaviors. We are doing the first two components at 40 clinical centers throughout the U.S., to enhance recruitment in medically underserved areas and

among minority populations.

The controlled clinical trial is evaluating three interventions: the effect of a low-fat dietary pattern on prevention of breast and colon cancer and coronary heart disease; the effect of hormonal replacement therapy on prevention of coronary heart disease and osteoporotic fractures; and the effect of calcium and vitamin D supplementation on prevention of osteoporotic fractures and colon cancer. We will offer women, who are ineligible or unwilling to participate in the



clinical trial, the opportunity to enroll in the concurrent long-term observational study that will delineate new risk factors and biological markers for diseases in women. The third part of WHI, the community prevention study, is aimed at evaluating strategies to achieve adoption of health behaviors including improved diet, nutritional supplementation, smoking cessation, increased physical activity, and early disease detection. We are conducting it with the Centers for Disease Control and Prevention through grants with their Community Prevention Centers.

The project is progressing well since it began in 1991: 16 vanguard centers began recruitment of volunteer participants in September 1993, and in February 1995 began recruitment of an additional 24 clinical centers. As of January 31, 1996, with two years remaining for recruitment efforts, the study has 45,974 women participating. As noted on the chart on the previous page,

the goal for enrollment of minorities is 20 percent (based on representation in the U.S. population). So far, we have reached 88 percent of this goal. Although scheduled for completion in 2004, we will publish results before that point as scientific data is available and analyzed. The budget to continue the Women's Health Initiative in FY 1997 is \$56.819 million.

The Office of Research on Minority Health

Minorities at all stages of life suffer poorer health and higher rates of premature death than the majority population. With some conditions, such as asthma and AIDS, we know a good deal about why minority populations are the hardest hit; we know less about how to reduce the disproportionate burden of these illnesses. With other conditions, such as lupus and certain cancers, it is still unclear why they disproportionately affect minorities.

The Office of Minority Research (ORMH) recognizes this disparity in health status and that research has much to contribute to closing the gaps between minority and nonminority populations. With a trans-NIH mission, the ORMH focus is twofold: to support and promote biomedical research aimed at improving the health status of minority Americans across the lifespan and to support and promote programs aimed at expanding participation of under-represented minorities in all aspects of biomedical and behavioral research. The ORMH works in partnership both with grassroots organizations in minority communities and with the scientists and program experts in the NIH ICDs. Support for studies and programs, as pilot projects, is subjected to rigorous scientific scrutiny and ongoing assessments by the Office. Successful pilot projects will ultimately become part of the research portfolios of the ICDs, freeing ORMH funds to support new pilot projects in other areas of need.

The budget request for the ORMH is \$9.134 million for FY 1997. A substantial portion of the budget will be directed toward outreach activities and collaborative programs with the ICDs. We will use these activities and programs to educate minority communities about important NIH policies and programs, coordinating supplemental programs, and outreach programs such as the National Cardiovascular Outreach Diffusion Network Initiative. We will direct funds to develop a strategic plan for educating minority Americans about the importance of being an organ donor.

The ORMH will continue to support its Minority Biomedical Training programs. One part of this portfolio is the Bridges to the Future program. They have designed it to increase the opportunities to enter careers in biomedical sciences for students who are members of under-represented minority populations. In addition, it fosters relationships between M.S. degree-granting minority institutions and research intensive Ph.D.-granting institutions. Another program is the Minority International Research Training Program. It supports international research and research training for undergraduate, graduate, and postgraduate minority students and faculties.

The ORMH is also committed to: increasing minorities in research study populations; enhancing the capacity of the minority community to participate in addressing its health problems; increasing collaborative research and research training programs between minority and majority institutions;

increasing the competitiveness and number of well-trained minority scientists applying for NIH funding; and developing an assessment tool for minority programs at NIH and a coordinated information system to link these programs.

The Minority Health Initiative

The Minority Health Initiative (MHI), in collaboration with NIH ICDs, supports a series of multi year research studies and a set of training programs. Its goals include increasing intramural and extramural research aimed at improving minority health, developing protocols for intervention in health behaviors affecting the longevity and quality of life for minorities and starting new programs to prepare minorities for careers in the biomedical sciences. Our budget request is for \$62.597 million in FY 1997.

The MHI portfolio consists of various activities resulting from recommendations from ORMH-sponsored consensus conferences aimed at filling the gap in knowledge related to minority health research and research training. One activity consists of multiple phases. The first phase, which is completed, was an assessment of NIH minority research and training programs. Phase II is underway, with and Phase III completing the entire assessment at the end of Fiscal Year 1997.

The MHI supports the Cooperative Community-based Perinatal Studies and Interventions in Minority Populations in the District of Columbia initiatives. Their goal is to effect a substantial reduction of infant mortality in Washington, D.C. We plan to develop a series of projects that will foster a better understanding of the determinants leading to high rates of infant mortality and low birth weight. In FY 1997 continued support will concentrate on research studies on the treatment of asthma, childhood lead exposure, and the prevalence, etiology, and pathogenesis of the leading causes of infectious diseases impeding childhood development, especially in hearing, speech and language development.

The MHI, in FY 1997, will continue support for eight projects in the Minority Youth Initiative that focus on strategies for decreasing violence-related injuries and deaths and unintended pregnancies in minority youths aged 10-18. As part of the Young Adult Initiative, ongoing intramural and extramural research studies relating to health problems and behaviors of young minority adults include kidney disease, hypertension, diabetes, obesity, hemochromatosis, glaucoma, lupus, AIDS, and alcohol related morbidity and mortality and oral health. Also, we will provide continued funding for Exploratory Centers for Research on health Promotion in Older Minority Populations. These centers study diseases and conditions leading to ill health and disability in the aged minority population.

The MHI plans, in FY 1997, to expand and strengthen programs aimed at creating minority research institutions that will be role models for other minority institutions. Like the WHI, the MHI supports the NIH policy to include minorities as subjects in all NIH-supported clinical research projects. We will also provide support through minority research supplements to attract more minorities into biomedical research careers and to promote independent research by minority investigators. We will provide financial support to the ICDs for technical assistance workshops on the grant application process and to minority researchers wishing to attend them. The MHI

will fund the continued development of the Coordinated Research and Training Information System. This system links various minority research and training programs at NIH with similar programs supported at other institutions such as the National Science Foundation. The system will increase the awareness of minority scientific research and research training programs for students, faculty, and program administrators; provide tracking of minority individuals pursuing careers in biomedical or behavioral research; and gather useful information about minority programs and identify factors leading to success.

The Office of Behavioral and Social Sciences Research

The NIH established the Office of Behavioral and Social Sciences Research (OBSSR) to recognize the important role these factors play in influencing health, along with genetic, physiologic, and environmental variables. The office will emphasize the integration of behavioral and social science's knowledge with biomedical knowledge to accelerate the understanding and treatment of physical and mental illnesses that are of interest to all NIH research components.

The OBSSR provides leadership and direction for the development of a trans-NIH plan to increase the scope of and support for behavioral and social science research; to define an overall strategy for the integration of these disciplines across NIH institutes and centers; to develop initiatives to stimulate research in the behavioral and social sciences arena and integrate a bio-behavioral perspective across the research areas of NIH; and to promote studies to evaluate the contributions of behavioral, social and lifestyle determinants in the development, course, treatment, and prevention of illness and related public health problems. Our budget request for the OBSSR in FY 1997 is \$2.348 million.

Although the office has only been operating since July 1995, many activities are well underway. The OBSSR has developed a draft definition of behavioral and social science. Once reviewed and refined, we will use it across NIH to evaluate and monitor funding in this area. This year we will prepare a report for Congress based on this definition to provide an overview of NIH's commitment to this area. In addition, the OBSSR will develop a strategic plan, in consultation with the scientific community, to help in charting the future direction of the office and establishing its priorities. In FY 1997, the OBSSR will continue to use part of its budget to fund research grants, workshops and conferences, in consultation with several NIH institutes and centers. For example, in 1995, the office funded 28 research project and ten conferences and workshops that involved 16 NIH institutes and centers. These projects ranged from basic animal research to epidemiologic studies. FY 1997 research funding may be directed at specific research areas targeted in the strategic plan. The office plans to work closely with all NIH institutes and centers to enhance their behavioral and social sciences research portfolios and help them in identifying promising research directions that they should support. Emphasis will be placed on research that cuts across institute boundaries to foster trans-NIH collaborations.

The Office of Science Education

We are establishing the Office of Science Education (OSE) in FY 1996 to centralize and refocus activities previously ongoing in several OD offices (the Office of Education, the Loan Repayment and Scholarship Programs, and the Office of Science Education Policy). We have charged the office with advising and coordinating NIH activities in intramural research training and science education with the NIH ICDs; planning and carrying out various programs, both nationally and locally, to improve science education and science literacy especially on biomedical and health sciences; starting programs that strengthen NIH-wide intramural research training, including recruitment and mentoring of trainees; and conducting evaluations and outcome assessments to find out what improvements we can make to the programs. The budget request for Science Education for FY 1997 is \$1.759 million.

For FY 1997, the office will continue to be the central focus for the development and coordination of science education policies and activities. The OSE will support several innovative programs that will address areas and audiences typically overlooked by traditional research training programs. These programs include the Science Alliance for local elementary school teachers and students; the NIH Speakers Bureau; the development of a worldwide web page for science education; the Howard Hughes student internship program, and the Science Education Partnership Awards (SEPA). Two public programs to continue include the NIH Mini-Med School and the Science in the Cinema film festival.

The largest grant program involving the OSE is the SEPA program which the National Center for Research Resources administers. These grants support the evaluation and national distribution of existing science education programs. The OSE will also be exploring a national science education curriculum for K-12 and will continue to locally support programs that train scientists who wish to participate in classroom education. Also planned will be modifications to the very successful Mini-Med School on Capitol Hill and at Ballou Math, Science, and Technology Academy in the District of Columbia. The office will continue its collaborative relationship with the ORWH to develop science education activities that encourage young women and individuals from traditionally underrepresented populations to pursue careers in life sciences.

The Office, in FY 1997, will continue to assess and monitor recruitment and retention trends resulting from intramural training programs, especially of postdoctoral and clinical fellows. The quality and efficacy of these programs is continually being evaluated. Funding will continue to support the recruitment of groups of underrepresented populations, particularly women and minorities, in the biomedical sciences. In addition, the OSE will provide support for the accreditation of clinical training programs and continuing medical education.

The OSE has assumed responsibility for the NIH Loan Repayment and Scholarship Programs. In FY 1997, the Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds will provide 15 awards, up to \$20,000 annually. The awards are for the repayment of the educational debt of awardees if they agree to conduct clinical research as NIH employees. For fifteen students who agree to pursue academic programs in the sciences or a related discipline, we will make scholarship awards under the Undergraduate Scholarship Program for

Individuals from Disadvantaged Backgrounds. Congress has statutorily mandated that scholars under this program agree to serve as NIH employees after graduation one year for each year of scholarship support received. The General Loan Repayment Program awards contracts to physicians and scientists engaged in both basic and clinical research endeavors. Its purpose is to recruit and retain health professionals in nontrainee intramural positions and consider them for permanent and/or tenure track positions. The maximum educational loan repayment is \$20,000 annually. The program also provides Federal tax reimbursements of 39 percent of the loan payments. This compensates for the increased Federal tax burden resulting from the receipt of loan payments. The Loan Repayment Program request for FY 1997 is \$2.9 million.

The Office of Alternative Medicine

The Office of Alternative Medicine (OAM) provides a central NIH focus for a research area germane to all NIH components. Alternative medicine is becoming increasingly popular in the industrialized world and research might help in identifying new effective approaches to the prevention and cure of disease. Generally, we define alternative medicine as practices used for the prevention and treatment of disease that we do not teach widely in medical schools, nor generally available inside hospitals. More than 80 percent of those who used unconventional practices in 1990 used these practices along with conventional medicine. In the U.S., one out of every three Americans saw alternative health care practitioners in 1990, paying over \$13 billion for these services. Surveys show that 50 percent of patients with cancer use unconventional practices at some point during their illness, and more than 50 percent of conventional physicians use or refer patients for alternative medical treatments in the U.S.

We charged the OAM with the evaluation of alternative medical treatment modalities; investigating and evaluating the efficacy of alternative treatments, establishing an information clearinghouse to provide information to the public; and supporting research training in alternative and complementary medical practices. In late FY 1995 we appointed a new Director and reorganized the office to focus its activities on specific elements of the Congressional mandate.

The budget request for the OAM is \$5.694 million. In 1993, the NIH Institutes awarded \$13 million in grants related to alternative medicine, showing the trans-NIH interest of this area. During FY 1997, the OAM intends to increase its funding for 10 national clinical research centers, co-funded by four other NIH components. These Centers form the foundation for conducting alternative medicine research and for providing mechanisms to support future collaborative research efforts in complementary and alternative medical practices. Areas under study include HIV/AIDS, cancer, addictions, asthma and immunologic disorders, women's health, general medical conditions, geriatrics, stroke and neurological conditions, and several areas in the study of pain.

In FY 1997, the office will continue to support a postdoctoral training awards program and to provide collaboratively funding for alternative medicine studies supported by the NIH institutes and centers. Collaborations will continue with the National Library of Medicine to add medical keywords and MeSh headings to their MEDLINE electronic database to improve access to information in the medical literature about alternative medicine. Several new initiatives planned

for FY 1997 include the establishment of an intramural research training program for clinical and preclinical investigators that will integrate scientific methodology with alternative practices; development of extramural training programs with medical schools and research institutes; the acceleration of database development and evaluation activities for information dissemination; facilitate and support public and private partnerships interested in complimentary and alternative medicine; and to provide increased support in collaboration with NIH institutes and centers for newly initiated research.

Other OD Offices

As part of the OD Operations, several Offices provide advice to the NIH Director, policy direction to the NIH research community, and administration of centralized support services essential to the daily operation of the NIH. The budget request for these operational offices for FY 1997 is \$43.210 million. Certain special emphasis program areas such as the Laboratory for Diagnostic Radiology Research, the Office of Rare Diseases Research, the Office of Dietary Supplements, the Loan Repayment Program, and the Academic Research Enhancement Award (AREA) are subsumed in these offices. These offices are also discussed below. Their budget request is \$19.807 million for FY 1997.

♦ The Office of Extramural Research

The Office of Extramural Research (OER) advises the NIH Director and provides guidance to the ICDs on the management of extramural research. Reviews of regulations, policies, and procedures on the effective stewardship of extramural research and training programs, peer review of extramural awards, and grants administration are carried out by the OER. The Office plays a major role in monitoring compliance with certain conditions placed on extramural awards such as the protection of human subjects, the welfare of animals, the inclusion of women and minorities in study populations, compliance with mandated patent policies and procedures, and the appropriate ethical conduct of research at NIH awardee institutions. Efforts continue, in FY 1997, to focus on computer systems design programming and systems maintenance of NIH's centralized extramural grants database and extramural staff training.

The OER also manages the Academic Research Enhancement Award (AREA) program. This special emphasis program area receives funding to provide an opportunity for educational faculty from non-intensive research institutions, to participate in biomedical and behavioral research efforts. The grants provide support for new or expanded health-related research projects at undergraduate colleges and universities where many of America's research scientists receive their degree. In FY 1997 the budget request for the AREA program is \$13.592 million which would permit the award of an 143 awards, an additional 13 above the FY 1996 level.

◆ The Office of Intramural Research

The Office of Intramural Research (OIR) primarily oversees the conduct of biomedical research in the NIH's research laboratories and clinics. It ensures that NIH maintains an environment that fosters the highest possible quality of research. In carrying out this mandate, the OIR oversees and formulates policies for the recruitment and retention of an outstanding and diverse group of scientists. The OIR works to develop new programs that encourage communication and exchange of new knowledge between scientists. OIR sponsors many weekly seminars with invited speakers throughout the year, publishes a bimonthly magazine called *The Catalyst*, maintains a bulletin board, and participates in special interest groups and science round tables. In addition, it promulgates policies and evaluation measures to strengthen the conduct of research and ethics in science and to protect human subjects and laboratory animals at NIH. The OIR also has responsibility for allocating laboratory space and for addressing environmental concerns within the laboratories.

One component of the OIR is the Laboratory of Diagnostic Radiology Research (LDRR) which has developed an extensive multi-disciplinary approach to the application of various imaging techniques to biomedical research and clinical care. These diverse areas include magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, single photon emission computerized tomography, and computerized tomography. The LDRR fosters increased collaboration among research groups involved in imaging research at the NIH. In FY 1997 the LDRR will continue its research initiatives in Molecular Imaging, Functional and Metabolic Imaging, Technical Development of new diagnostic techniques and Image Processing. Work continues in FY 1997 on new techniques for evaluating women with early stages or at high risk of having breast cancer. Investigations will proceed in areas of early detection and monitoring of therapeutic responses of malignancy, acquired immunodeficiency diseases, tissue characterization, transplantation rejection, and auto immune disorders. A primary goal of the LDRR, in addition to a research laboratory, is the training of young scientists for research careers in medical imaging. Finding new ways to recruit individuals with recent residency training in nuclear medicine or radiology presents a challenge to the LDRR in FY 1997 as FTEs are reduced at the NIH. The budget request for FY 1997 for the LDRR is \$1.915 million.

A new component of the OIR is the Office of Technology Transfer (OTT). It provides guidance, advice, and policies on technology transfer to the Director, NIH, the ICDs, other PHS agencies, and to potential partners outside the government. The OTT is responsible for the patenting and licensing of NIH's intellectual property, facilitating receipts in royalty payments for NIH and other HHS agency staff, obtaining and enforcing domestic and foreign patents on NIH inventions, and assisting in the development and execution of Cooperative Research and Development Awards (CRADAs). Since NIH is the lead HHS Agency for technology transfer, OTT provides this service to all the NIH ICDs and to the Food and Drug Administration and the Centers for Disease Control and Prevention.

◆ The Office of Disease Prevention

The Office of Disease Prevention (ODP) provides the leadership, coordination, and support for disease prevention research and health promotion activities at NIH, including health promotion programs for employees. The Office serves as NIH's representative regarding all disease prevention research plus school-health, public health, nutrition, physical fitness, and environmental health issues. The Office interacts with the other Public Health Service Agencies, the President's Office of Science Technology and Policy, and with the academic and private sectors and advocacy groups.

The ODP's Office of Medical Applications of Research (OMAR) coordinates the synthesis and distribution of new research ready for use in the health care system. It carries out these activities using consensus development conferences of important health issues. The Women's Health Initiative (WHI), discussed earlier, is a large prevention study that the ODP coordinates.

We are transferring responsibility for the Office of Rare Disease Research (ORDR) from the Office of Science Policy to the ODP in FY 1996. The ORDR provides information on rare diseases and conditions and helps in the linkage of research investigators with research subjects and patients who are willing to participate in clinical research investigations. It does this by developing, implementing, and maintaining a centralized NIH database on rare diseases and distributes this information upon request. It also stimulates rare diseases research by supporting scientific workshops and symposia to identify research opportunities. The budget request for ORDR is \$0.750 million.

In FY 1996, we will establish the Office of Dietary Supplements (ODS) as part of the Office of Disease Prevention. In FY 1996, we hired the first Director who is coordinating and providing support for research on the health effects of dietary supplements. The budget request for FY 1997 is \$0.650 million. In FY 1997, the ODS begins developing its strategic plan and research support agenda. In addition, it will expand its opportunities to interact and exchange information with researchers throughout the country through sponsorship of workshops and conferences.

◆ The Office of Science Policy

We reorganized and streamlined the Office of Science Policy (OSP), formerly the Office of Science Policy and Technology Transfer, in FY 1996. Its focus is to provide the leadership, direction, and coordination for all phases of science policy and to address issues in areas where science interfaces with the society at-large. The OSP advises the NIH Director on a broad array of issues including social, legal, ethical, and economic implications resulting from developments in the biomedical and behavioral sciences and proposes policy approaches. The OSP centrally addresses major cross cutting science and biotechnology issues and serves as the focal point for NIH strategic planning. General

policies on recombinant DNA activities, managing the NIH rDNA Advisory Committees, and development of NIH policies and procedures on the safe conduct of rDNA activities come under the purview of the OSP.

Another major activity is the collaboration with ICDs and other OD components on the guidance and coordination of NIH's evaluation process and the administration of the one percent set-aside evaluation funds. The OSP prepares white papers, special studies and reports required by the OD and Congress, tackles special studies designed to develop and improve methods of evaluating NIH health research, and undertakes cross cutting evaluation research.

◆ **The Office of Legislative Policy and Analysis**

The Office of Legislative Policy and Analysis (OLPA) is an independent Office reporting directly to the Director, NIH. This Office plays an essential role in the policy-making process at NIH. Besides advising the NIH Director, OD staff, and the ICDs on the full range of legislative issues, the OLPA provides leadership and direction for NIH legislative analysis, development, and liaison. The Office plans and develops new legislative proposals and monitors their progress through the legislative process. It also assesses, monitors, and manages the NIH relationship with the NIH Congressional Authorizing and Appropriations Committees. The OLPA develops special reports and other studies concerning NIH interests, activities, and relationships and coordinates the preparation of congressional testimony before congressional committees or other groups.

◆ **The Office of Equal Opportunity**

The Office of Equal Opportunity (OEO) provides the leadership, guidance, and policy direction to all ICDs. It assists in ensuring that all programs, functions, and activities meet Federal equal employment opportunity statutes, laws and regulations. The OEO advises the NIH Director, OD staff, and the ICDs about the effective management of diversity and civil rights compliance. It also maintains a liaison role with NIH activities that administer programs to increase minority participation in biomedical research. Besides providing broad policy advice and guidance on affirmative action programs, the OEO serves as the operational center for formal discrimination complaints. In FY 1997, the NIH will begin widespread use of the informal complaints process with each ICD and the OD. It will also be evaluating, with the Office of Human Resource Management, the operation of a new NIH-wide alternative disputes resolution center.

◆ **The Office of Communications**

The Office of Communications (OC) plans and directs communications activities aimed at the media, public, Congress, biomedical institutions, and the medical professions. It strives to maintain the public's respect and trust for the NIH as a purveyor of science-

based health information and steward of the public's \$12 billion investment in biomedical research. The office also coordinates the public affairs and other communications activities of the ICDs.

For FY 1997, the Office will continue to oversee the expanded use of the Internet, including use of the NIH Home Page to convey health information prepared for the public and patients. The OC will also pursue the use of television pilots to inform the public about advances in biomedical research, disease prevention activities, and health care. The OC also plans a new project aimed at bringing health news and health education messages to members of the public who rely on smaller weekly and daily newspapers around the country.

♦ The Office of Community Liaison

In FY 1995, we created the Office of Community Liaison (OCL) to advise the Director, NIH on policies, programs, and issues involving the NIH and its neighbors. The OCL conducts and oversees studies, projects, and evaluations designed to address the problems, questions, and issues of concern to the communities including their environmental impact. The OCL, in FY 1997, continues to plan and direct activities aimed at promoting collaboration between the surrounding communities and the NIH. The Office ensures that community representation is present at all levels of design, review, and implementation of NIH activities that affect it. Efforts will continue to ensure that effective communication and collaboration on policy and programs involve the nearby community, the operating components of NIH, and the OD.

♦ Operational, Administrative, and Management Offices

Many other Offices in the OD are responsible for carrying out operation, administrative, and management functions. They provide leadership and guidance in all phases of management, administration, budget and financial management, information resources management, human resource management, management assessment, internal controls, grants and contracts management, acquisitions, logistics, property management, engineering services, safety, space and facilities management, and security operations.

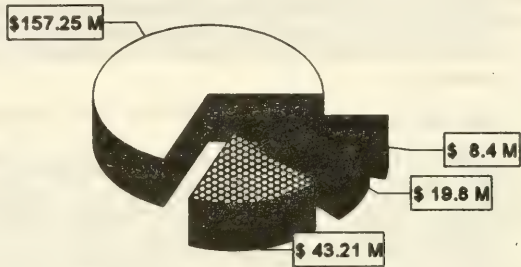
♦ Director's Discretionary Fund

In FY 1997, the NIH Director will continue to maintain a Director's Discretionary Fund (DDF) to enable him to respond quickly to new and emerging high priority research opportunities and health priorities. In addition, funds will support the Shannon Awards, the Director's Wednesday Afternoon Lecture Series and several other seminar events to further the exchange of scientific knowledge and discovery. The request for FY 1997 is \$8.442 million.

Overall Budget Policy

The FY 1997 budget request for the Office of the Director is \$226.913 million, which represents a decrease of \$6.977 million from the FY 1996 budget level of \$233.890 million.

Office of the Director FY 1997



Program Coordination



OD Operations

Special Emphasis Areas

Director's Discretionary Fund

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Mechanism

	1995		1996		1997	
	FTEs	Actual Amount	FTEs	Estimate Amount	FTEs	Estimate Amount
Research Management & Support....	749	\$214,234,000	657	\$233,890,000	657	\$226,913,000
OD Operations.....	(681)	(44,722,000)	(589)	(43,210,000)	(589)	(43,210,000)
Director's Discretionary Fund.....		(7,476,000)		(11,415,000)		(8,442,000)
Laboratory for Diagnostic Radiology Research.....	(10)	(1,767,000)	(9)	(2,015,000)	(9)	(1,915,000)
Office of Alternative Medicine.....	(8)	(5,374,000)	(12)	(7,486,000)	(12)	(5,694,000)
Academic Research Enhancement Award Program.....		(12,677,000)		(14,092,000)		(13,592,000)
Science Education.....	(4)	(1,696,000)	(4)	(1,879,000)	(4)	(1,759,000)
Research on Minority Health.....	(8)	(8,923,000)	(7)	(9,413,000)	(7)	(9,134,000)
Research on Women's Health.....	(15)	(12,505,000)	(14)	(17,203,000)	(14)	(17,103,000)
Women's Health Initiative.....	(17)	(56,915,000)	(16)	(56,819,000)	(16)	(56,819,000)
Minority Health Initiative.....	(2)	(58,210,000)	(2)	(62,797,000)	(2)	(62,597,000)
Loan Repayment Program.....		(954,000)		(2,963,000)		(2,900,000)
Office of Rare Disease Research.....	(2)	(750,000)	(2)	(1,250,000)	(2)	(750,000)
Office of Dietary Supplements.....		(---)		(1,000,000)		(650,000)
Office of Behavioral & Social Sciences Research.....	(2)	(2,265,000)	(2)	(2,348,000)	(2)	(2,348,000)
Total Budget Authority.....	749	214,234,000	657	233,890,000	657	226,913,000
Funds reimbursed or directly supporting ICDS.....		(158,577,000)		(177,131,000)		(170,493,000)

Note: Includes FTEs associated with NIH AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DHHS - National Institutes of Health

Office of the Director
Allocation by Mechanism 1/

(Dollars in thousands)

	<u>FY 1995 Actual</u>	<u>FY 1996 Estimate</u>	<u>FY 1997 Estimate</u>
Research Grants:			
Research Projects.....	\$41,738	\$53,334	\$89,322
Research Centers.....	---	---	---
Other Research.....	---	---	---
Total, Res. Grants.....	\$41,738	\$53,334	\$89,322
Training.....	25,470	28,984	24,552
R&D Contracts.....	90,415	94,813	56,619
Intramural Research.....	2,721	4,978	4,815
Res. Mgmt. and Support.....	8,418	9,321	9,145
Cancer Control.....	---	---	---
Construction.....	---	---	---
Total, ICD.....	168,762	191,430	184,453
OD Operations.....	45,472	42,460	42,460
Total.....	214,234	233,890	226,913

1/ This represents a breakout of the OD's budget as it is ultimately expended by mechanism.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Activity
(Dollars in thousands)

	1993 1/ Actual FTEs Amount	1994 1/ Actual FTEs Amount	1995 1/ Actual FTEs Amount	1996 1/ Estimate FTEs Amount	1997 1/ Estimate FTEs Amount	Change FTEs Amount
Research Management and Support.....	716 \$175,311	700 \$202,539	749 \$214,194	657 \$233,890	657 \$226,913	---
Unobligated balance start of year.....	---	---	---	---	---	---
Unobligated balance end of year.....	---	---	---	---	---	---
Subtotal obligations.....	175,311	202,539	214,194	233,890	226,913	-6,977
Unobligated balance lapsing.....	70	146	40	---	---	---
Total budget authority...	716 \$175,381	700 \$202,685	705 \$214,234	657 \$233,890	657 \$226,913	-6,977
Funds reimbursed or directly supporting ICDs.....	(127,808)	(151,586)	(158,577)	(177,131)	(170,493)	(-6,638)

1/ The FY 1993 actual, FY 1994 actual, FY 1995 actual, the FY 1996 estimate, and the FY 1997 estimate excludes \$9,277,000, \$7,334,000, \$5,000,000, \$5,000,000 and \$5,000,000 respectively, in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Summary of Changes

1996 Estimated budget authority.....	\$233,890,000
1997 Estimated budget authority.....	<u>226,913,000</u>
Net Change.....	-6,977,000

	1996 Current		Change from Base	
	Estimate	Base Budget	Budget	Authority
	FTEs	Authority	FTEs	Authority
<u>Changes:</u>				
A. <u>Built-in:</u>				
1. Annualization of FY 1996 pay raise.....		\$31,780,000		+\$283,000
2. Within grade increase.....		31,780,000		+493,000
3. FY 1997 Pay Raise.....		31,780,000		+731,000
4. FECF.....		31,780,000		+1,000
5. Increased cost of services and supplies.....		44,487,000		+4,326,000
6. Service and Supply Fund increase...		4,756,000		+120,000
Subtotal.....				+5,954,000
B. <u>Program:</u>				
1. Office of Research on Women's Health.....	14	\$17,203,000		-\$100,000
2. Office of Research on Minority Health.....	8	9,413,000		-279,000
3. Loan Repayment Program.....		2,963,000		-63,000
4. Science Education.....	4	1,879,000		-120,000
5. Minority Health Initiative.....	2	62,797,000		-200,000
6. Academic Research Enhancement Award Program.....		14,092,000		-500,000
7. Laboratory of Diagnostic Radiology Research.....	9	2,015,000		-100,000
8. Director's Discretionary Fund.....		11,415,000		-2,973,000
9. Office of Rare Disease Research...	2	1,250,000		-500,000
10. Office of Dietary Supplements...		1,000,000		-350,000
11. Office of Alternative Medicine...	8	7,486,000		-1,792,000
12. Administrative Reductions.....				-5,954,000
Subtotal.....				-12,931,000
Total Changes.....				-6,977,000

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Object

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Total compensable workyears:	657	657	---
Full-time equivalent employment.....	657	657	---
Full-time equivalent of overtime and holiday hours.....	5	5	---
Average ES salary.....	\$108,635	\$111,079	+\$2,444
Average GS/GM grade.....	11	11	11
Average GS/GM salaries.....	\$47,055	\$48,114	+\$1,059
Average salary, grades established by act of July 1, 1944 (42 USC 207).....	\$84,778	\$86,686	+\$1,908
Personnel Compensation:			
Full-time permanent.....	\$25,265,000	\$26,241,000	+\$976,000
Other than full-time permanent....	1,574,000	1,632,000	+58,000
Other personnel compensation.....	550,000	570,000	+20,000
Special personnel service payments.....	<u>138,000</u>	<u>143,000</u>	<u>+5,000</u>
Total, personnel compensation...	27,527,000	28,586,000	+1,059,000
Personnel benefits.....	4,253,000	4,702,000	+449,000
Travel and transportation of persons.....	307,000	330,000	+23,000
Transportation of things.....	69,000	73,000	+4,000
Rent, communications and utilities..	1,270,000	1,361,000	+91,000
Printing and reproduction.....	614,000	651,000	+37,000
Consultant Services.....	1,375,000	770,000	-605,000
Other services.....	14,188,000	12,057,000	-2,131,000
Purchasing from government accts....	81,736,000	117,905,000	+36,169,000
Operation of GOCOs.....	---	---	---
R&D contracts.....	94,813,000	56,619,000	-38,194,000

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Supplies and materials.....	\$738,000	\$689,000	-\$49,000
Equipment.....	3,000,000	3,170,000	+170,000
Grants, subsidies and contributions..	<u>4,000,000</u>	<u>---</u>	<u>-4,000,000</u>
Total budget authority by object.....	233,890,000	226,913,000	-6,977,000
Funds reimbursed or directly supporting ICDs.....	(177,131,000)	(170,493,000)	(-6,638,000)

Note: These amounts represent funds reimbursed to the ICDs for grant awards.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Object

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Total compensable workyears:	657	657	---
Full-time equivalent employment.....	657	657	---
Full-time equivalent of overtime and holiday hours.....	5	5	---
Average ES salary.....	\$108,635	\$111,079	+\$2,444
Average GS/GM grade.....	11	11	11
Average GS/GM salaries.....	\$47,055	\$48,114	+\$1,059
Average salary, grades established by act of July 1, 1944 (42 USC 207).....	\$84,778	\$86,686	+\$1,908
Personnel Compensation:			
Full-time permanent.....	\$25,265,000	\$26,241,000	+\$976,000
Other than full-time permanent....	1,574,000	1,632,000	+58,000
Other personnel compensation.....	550,000	570,000	+20,000
Special personnel service payments.....	<u>138,000</u>	<u>143,000</u>	<u>+5,000</u>
Total, personnel compensation...	27,527,000	28,586,000	+1,059,000
Personnel benefits.....	4,253,000	4,702,000	+449,000
Travel and transportation of persons.....	307,000	330,000	+23,000
Transportation of things.....	69,000	73,000	+4,000
Rent, communications and utilities..	1,270,000	1,361,000	+91,000
Printing and reproduction.....	614,000	651,000	+37,000
Consultant Services.....	1,375,000	770,000	-605,000
Other services.....	14,188,000	12,057,000	-2,131,000
Purchasing from government accts....	3,418,000	4,031,000	+613,000
Operation of GOCOs.....	---	---	---
R&D contracts.....	94,813,000	56,619,000	-38,194,000

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Supplies and materials.....	\$738,000	\$689,000	-\$49,000
Equipment.....	3,000,000	3,170,000	+170,000
Grants, subsidies and contributions..	<u>82,318,000</u>	<u>113,874,000</u>	<u>+31,556,000</u>
Total budget authority by object.....	233,890,000	226,913,000	-6,977,000
Funds reimbursed or directly supporting ICDs.....	(177,131,000)	(170,493,000)	(-6,638,000)

Note: These amounts represent funds reimbursed to the ICDs for grant awards.

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Office of the Director

Administrative Costs

	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>	<u>Change</u>
Personnel Compensation:			
Full-time permanent (11.1).....	\$25,265,000	\$26,241,000	+\$976,000
Other than full-time perm. (11.3) ..	1,574,000	1,632,000	+58,000
Other personnel compen. (11.5)....	550,000	570,000	+20,000
Special personnel service payments (11.8).....	<u>138,000</u>	<u>143,000</u>	<u>+5,000</u>
Total Personnel Comp. (11.9).....	27,527,000	28,586,000	+1,059,000
Civilian Personnel Benefits (12.1) ..	4,253,000	4,702,000	+449,000
Benefits to Former Personnel (13.0) .	---	---	---
Travel (21.0).....	307,000	330,000	+23,000
Transportation of Things (22.0).....	69,000	73,000	+4,000
Rental Payments to Others (23.2)....	---	---	---
Communications, Utilities, and Miscellaneous Charges (23.3).....	1,270,000	1,361,000	+91,000
Printing and Reproduction (24.0)....	614,000	651,000	+37,000
Consulting Services (25.1).....	1,375,000	770,000	-605,000
Other Services (25.2).....	14,188,000	12,057,000	-2,131,000
Purchase of Goods & Services from other Government Accounts (25.3)...	81,736,000	117,905,000	+36,169,000
Operation of GOCOs (25.4).....	---	---	---
Supplies and Materials (26.0).....	<u>738,000</u>	<u>689,000</u>	<u>-49,000</u>
Total.....	132,077,000	167,124,000	+35,047,000

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Administrative Costs

	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>	<u>Change</u>
Personnel Compensation:			
Full-time permanent (11.1).....	\$25,265,000	\$26,241,000	+\$976,000
Other than full-time perm. (11.3) ..	1,574,000	1,632,000	+58,000
Other personnel compen. (11.5)....	550,000	570,000	+20,000
Special personnel service payments (11.8).....	<u>138,000</u>	<u>143,000</u>	<u>+5,000</u>
Total Personnel Comp. (11.9).....	27,527,000	28,586,000	+1,059,000
Civilian Personnel Benefits (12.1) ..	4,253,000	4,702,000	+449,000
Benefits to Former Personnel (13.0) ..	---	---	---
Travel (21.0).....	307,000	330,000	+23,000
Transportation of Things (22.0).....	69,000	73,000	+4,000
Rental Payments to Others (23.2)....	---	---	---
Communications, Utilities, and Miscellaneous Charges (23.3).....	1,270,000	1,361,000	+91,000
Printing and Reproduction (24.0)....	614,000	651,000	+37,000
Consulting Services (25.1).....	1,375,000	770,000	-605,000
Other Services (25.2).....	14,188,000	12,057,000	-2,131,000
Purchase of Goods & Services from other Government Accounts (25.3)...	3,418,000	4,031,000	+613,000
Operation of GOCOs (25.4).....	---	---	---
Supplies and Materials (26.0).....	<u>738,000</u>	<u>689,000</u>	<u>-49,000</u>
Total.....	53,759,000	53,250,000	-509,000

NATIONAL INSTITUTES OF HEALTH

Office of the Director

SIGNIFICANT ITEMS IN HOUSE AND SENATE
APPROPRIATIONS COMMITTEE REPORTS1996 House Appropriations Committee Report LanguageItem

Cardiovascular disease and diabetes - ...The House in its report 104-209, page 79 states that The Committee is pleased with the collaborative efforts already underway between the Office of Research on Women's Health (ORWH) and NIDDK to co-fund research focusing on cardiovascular disease in women with diabetes. Diabetes is one of the leading risk factors for coronary artery disease among women between the ages of 30 and 55 who have Type I diabetes. The Committee encourages the ORWH to develop and pursue new projects that could lead to the prevention and control of diabetes and its potentially devastating consequences in women".

Action Taken or to be Taken

NIH has enhanced its research on the effects of diabetes on cardiovascular disease, especially in females. To better understand vascular effects, the ORWH and NIDDK are co-funding a study of carotid artery ultrasound tests in a national cohort of patients with Type I diabetes. One of the risk groups being studied in the Diabetes Prevention Program are women with a history of gestational diabetes mellitus. The NHLBI supports the Insulin Resistance Atherosclerosis Study which examines the relationship of insulin and insulin resistance to cardiovascular disease and its risk factors. NHLBI also supports a study of the clinical course of coronary heart disease in Black women that includes an analysis of coronary artery disease and diabetes. The incidence of diabetes and cardiovascular disease in Mexican Americans and non-Hispanic whites is being examined in another NHLBI funded study. Work at the NIA focuses on the basic metabolic processes related to aging, diabetes and vascular disease. ORWH continues to work with ICDs on development of additional projects, and has highlighted diabetes in women as a priority for FY96 funding.

Item

Lymphangioleiomyomatosis [LM] - ...The House in its report 104-209, page 79 states that The Committee believes that an important step in finding a cure for this disease may be through the establishment of a national registry for LAM patients which would allow the pooling of experience from the largest number of individuals possible. The Committee, therefore,

encourages the Office of Research on Women's Health, in conjunction with NHLBI and the Office of Rare Disease Research, to fund research in this area, including a possible national patient registry*.

Action Taken or to be Taken

To address lymphangi leiomyomatosis (LAM), the Heart, Lung, and Blood Institute (NHLBI) convened a working group of scientists to review what is currently known about the disease and to identify research needs. As a follow-up to the meeting, the NHLBI, in collaboration with the Office of Research on Women's Health (ORWH) and the Office of Rare Disease Research (ORDR), issued a program announcement to encourage the scientific community to submit research grant applications to study the molecular and cellular mechanisms of LAM. The NHLBI anticipates receiving investigator-initiated grant applications for a national patient registry and tissue repository for possible funding in FY 97. If an applicant is successful, the NHLBI will be joined by ORWH and ORDR in sponsoring the registry. The NHLBI also produced a fact sheet on LAM, written specifically for LAM patients, their families and friends. A LAM research laboratory has been established in the NHLBI intramural program to conduct both basic and clinical studies of LAM. The first LAM patients have now been enrolled in a clinical protocol at the NIH clinical center. A close working relationship between the recently organized LAM Foundation and the NHLBI and ORDR staffs has been established to work together toward common goals, and ORWH will continue to collaborate in these efforts.

Item

Diabetes - ...The House in its report 104-209, page, 79/80 states that the Committee is pleased with the collaborative efforts that the Office of Research on Minority Health (ORMH) has pursued with NIDDK on research to promote the health of minorities, particularly on the genetics of diabetes and the treatment and prevention of the disease in minority populations. The Committee urges the ORMH to continue its support of cooperative efforts with NIDDK through the Minority Health Initiative, and to continue to focus specifically on the genetics of diabetes and the treatment and prevention of the disease. The Committee also encourages the ORMH through the Minority Health Initiative to explore collaborative opportunities with the Centers for Disease Control and Prevention to support the expansion of the diabetes control program.

Action Taken or to be Taken

Since its inception, the ORMH has collaborated with NIDDK in various ongoing initiatives to promote research on a range of minority populations suffering from diabetes. Funding by the ORMH was begun in FY 1994 for the Gestational Diabetes Component of Diabetes Prevention Program. The overall recruitment goal for the Diabetes Prevention Program is 3000-4000 subjects, of whom 50 to 60 percent will be minorities. In FY 1995, ORMH funds provided support to two centers that have major involvement in the minority gestational diabetes mellitus (GDM) component of the trial. In addition, ORMH is contributing to research in the area of the genes that are related to the development of obesity, many of which may also be tied to the

pathology of diabetes. The ORMH is looking forward in FY 1996-1997 to collaboration with the Centers for Disease Control and Prevention relating to screening for undiagnosed diabetes in the population (minorities are disproportionate in this category).

Item

Integrative medical sciences - ...The House in its report 104-209, page 82, states that the NIH is encouraged to foster implementation of programs to provide sound peer review and funding of integrative medical sciences projects conducted in intact vertebrates including humans. Enhancement is needed both in the number of investigator-initiated research grants and in training grants designed to replenish the pool of scientists with the skills to conduct research at the level of the intact animal. Restoration of our national capacity to advance the understanding of human function and disease in the integrative context is essential to developing suitable preventions, treatments and diagnostic procedures.

Action Taken or to be Taken

In its mission to maintain and improve the health and well being of the American people, the NIH fosters the development and application of innovative research strategies in the biomedical and behavioral sciences; provides research resources; sponsors the training of research personnel; and evaluates, validates, and disseminates new information about medicine and health. The NIH is confident that the use of a combination of laboratory animals and mathematical, computer, physical, cell and tissue culture models--in a complementary and interactive manner--will most effectively advance our understanding of the human body, to extend healthy life, and to reduce the burdens of illness and disability.

Item

Diagnostic radiology - ...The House in its report 104-209, page 82, states that with the Committee's support, research is now underway at the Laboratory for Diagnostic Radiology Research to more accurately detect early stages of breast and ovarian cancer, especially among younger women. As a central focus for radiology research, the intramural laboratory not only responds to these types of emerging health issues, but can also enhance, through non-invasive imaging procedures, the research capabilities of other intramural research teams as well as assist extramural programs in identifying promising areas of research. The Committee encourages this type of activity and urges NIH to continue its support for the laboratory".

Action Taken or to be Taken

The Laboratory of Diagnostic Radiology Research (LDRR) is presently involved in the development of new imaging techniques for the early detection of breast cancer and exploring new contrast agents that could be used to evaluate early stages of ovarian malignancy. LDRR has developed an extensive collaboration in Magnetic Resonance Imaging and Spectroscopy with

several intramural imaging laboratories and extramural university departments in the United States and abroad. LDRR will continue to explore other areas of imaging research that will impact on emerging health issues and the training of young scientists for a career in imaging research.

1996 Senate Report Language

Item

Office of Behavioral and Social Sciences Research - ...The Senate in its report 104-145, page 110 states that The Committee is pleased to learn that the Office of Behavioral and Social Sciences Research will soon be fully implemented. The Committee anticipates that the OBSSR will provide the necessary structure to promote, facilitate, and increase behavioral and social science research at the NIH. The Committee urges the OBSSR to work in partnership with other NIH institutes and outside organizations to develop research on testing psychosocial and behavioral interventions and strategies aimed at improving patient disease management, adherence to treatment, appropriate utilization of medical care, and promoting expanded quality of life.

Action Taken or to be Taken

The Office of Behavioral and Social Sciences Research officially opened in July, 1995. In FY 1995, OBSSR spent approximately \$2 million in collaborative activities with the NIH institutes and centers to sponsor research and conferences addressing social and behavioral factors related to health. These included projects on the prevention and treatment of childhood obesity, depression and coronary heart disease, aging and health, and a variety of other health-related topics. In FY 96, OBSSR took the lead in bringing together several NIH institutes and offices, the National Institute of Justice, the National Center of Child Abuse and Neglect and the Centers for Disease Control and Prevention to co-sponsor an RFA on violence against women and violence within the family. The purpose of this RFA is to support research aimed at improving our understanding of the nature and course of sexual and physical assault against women and family members. It will also support research on effective strategies to prevent such violence and to ameliorate the effects of such violence on its victims.

Future OBSSR activities include trans-NIH initiatives on basic behavioral and social science research that will provide the foundation for the development of effective psychosocial and behavioral intervention strategies leading to improved health and quality of life. In addition, OBSSR will work with NIH institutes and centers to incorporate research on behavioral and social factors in the study of diabetes, oral health and other important health concerns.

Item

Office of Behavioral and Social Sciences Research - ...The Senate in its report 104-145, page 110 states that The Committee notes with great interest the National Research Council report, "Meeting the Nation's Needs for Biomedical and Behavioral Scientists." This report recommends placing high priority on NRSA awards to behavioral scientists in order to address a shortage of

behavioral science researchers. The Committee expects the Director to provide an update during the fiscal year 1997 hearings on NIH's progress in implementing this recommendation and support for behavioral science researchers.

Action Taken or to be Taken

The Office of Behavioral and Social Sciences Research (OBSSR) recognizes the need to ensure a supply of well-trained behavioral and social scientists who can address important questions related to health. The office is working with the NIH institutes and centers to identify gaps in the NIH training activities related to behavioral and social science as well as opportunities for expanding and enhancing training for behavioral and social scientists. OBSSR will provide an update on NIH's progress toward improving training opportunities for behavioral and social scientists.

Item

Office of Rare Disease Research - ...The Senate in its report 104-145, page 110 states that The Committee recognizes the advances made in identifying the location of genes for rare and genetic diseases. The scientific research leading to the discovery of these genes is the result of many years of dedicated basic research. These discoveries have caused some confusion leading to the belief that treatment is or will soon be readily available through gene therapy. The Committee requests that the Office of Rare Disease Research working jointly with the National Center for Human Genome Research develop plans for establishing an information center to respond to inquiries about rare and genetic disorders.

Action Taken or to be Taken

The Office of Rare Disease Research is planning to establish an Information Center for Rare and Genetic Disorders at the National Institutes of Health. The office and the National Center for Human Genome Research continue to develop plans for establishing such an information center to respond to inquiries about rare and genetic disorders. This center will serve as a gateway to existing information and will also develop new information to be included in an interactive home page on the Internet. Information to be made available to health care providers and the public include the following: (1) information about the disease or condition; (2) location of genetic counseling centers available for consultation; (3) summary and location of current and planned research related to rare and genetic disorders; (4) names, location, and types of printed or audiovisual materials made available by voluntary patient support groups; (5) assist in the development of disease specific fact sheets; and (6) provide a toll free 800 phone number to respond to inquiries about rare and genetic disorders.

Item

Clinical Research - ...The Senate in its report 104-145, page 112 states that The Committee urges the NIH Director to build upon steps undertaken to strengthen and expand clinical research training opportunities; to expand the General Clinical Research Program and GCRC training opportunities; and to develop a loan forgiveness program available to both intramural and

extramural scientists who pursue careers in clinical research. The Committee views this matter with such importance that it would consider a proposal from the Director to utilize the 1-percent transfer authority to implement the changes in fiscal year 1996.

Action Taken or to be Taken

The NIH Director is firmly committed to the vitality of clinical research as an essential part of the NIH mission to improve health through biomedical research. The NIH shares the Committee's views of the importance of clinical research. For fiscal year 1996, the NIH is planning to use the one percent transfer authority to support research initiatives that have broad applicability and cut-across the individual ICDs' portfolios. It is recognized that clinical research issues are central to the missions of the ICDs and they are accounted for within the ICDs' budgets. However, the one percent transfer authority also might be used in special collaborative projects such as the neurobiology consortium involving NINDS, NIMH, NIAAA, and NIA for research on the development of the nervous system, neuronal maintenance and repair, neurodegeneration, growth factors, and addictions.

In July 1995 the NIH Director established the Panel on Clinical Research to discuss the challenges facing academic health centers and clinical investigators. It is composed of distinguished individuals from academia, industry, and government. The Panel plans to make recommendations regarding the support for clinical research, and improvement of research training in clinical medicine.

The research and training activities in the General Clinical Research Centers program have been expanded. For example, new satellite GCRCs have been established in both specialized and pediatric hospitals. Additional support will be provided in FY 1996 to further increase the patient research capacity of the network of GCRCs. Due to the increasing impact of managed care on clinical research, GCRCs now provide support for more late Phase II and Phase III clinical trials as well as Phase I. In the training arena, the NIH has created a formal training program for the clinical associates in the NIH Research Clinical Center that includes a core curriculum in clinical research composed of four modules that cover scientific, ethical, legal, and social issues relevant to clinical research. The loan forgiveness program currently supports 19 physicians in the intramural program and it is anticipated that an additional 10 physicians will be recruited in FY 96.

Item

Small Business Innovation Research Program - ...The Senate in its report 104-145, page 113 states that The Committee notes that a recent General Accounting Office Study (GAO/RCED95-59, "Small Business Innovation Research Program") has raised questions about the merit of small business innovation research projects funded by the National Institutes of Health [NIH]. The Committee directs the NIH to be prepared to provide an accounting of SBIR proposals submitted, their priority scores and funding status for fiscal years 1994 and 1995, during the fiscal year 1997 budget hearings.

Action Taken or to be Taken

The Small Business Innovation Research (SBIR) program at the NIH increased during fiscal years (FY) 1994 and 1995 in the amounts of \$7.2 million and \$47.9 million, respectively, for totals of \$125.5 million and \$173.4 million, respectively. The increase in FY 1994 occurred without a rise in the percentage of the extramural budget reserved for the program as specified by P.L. 102-564, dated October 28, 1992, the "Small Business Research and Development Enhancement Act of 1992." However, all but \$6.1 million of the expansion in FY 1995 happened as a result of the increase in the statutory percentage from 1.5 percent of the extramural budget to 2.0 percent. In FY 1997 the legislation requires a rise to 2.5 percent, where the percentage is scheduled to remain through the SBIR authorization period of FY 2000.

As requested by the committee, the NIH will provide an accounting of SBIR proposals reviewed and their priority scores and funding status for FY 1994 and FY 1995, during the FY 1997 budget hearings.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Estimate	1997 Amount Authorized	1997 Estimate
Office of the Director.....	Title IV, Section 402(b)	Indefinite	\$233,890,000	Indefinite	\$226,913,000

Funded Authorizations:

Total Budget Authority...	\$233,890,000	\$226,913,000
Funds reimbursed or directly supporting ICDs.....	(\$177,131,000)	(\$170,493,000)

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation 1/</u>
1988	\$59,819,000	\$71,389,000 2/	\$61,284,000	61,819,000
1989	59,578,000	71,578,000	65,578,000	72,201,000
1990	96,570,000	106,987,000	127,570,000	108,468,000 3/
1990 Sequester				-1,049,000
1991	82,975,000	106,175,000	77,975,000	97,651,000 4/
1991 Sequester				-1,000
1992	95,176,000	149,176,000	125,724,000	142,112,000 5/
1993	203,430,000	194,275,000	188,400,000	190,325,000 6/
1994	234,907,000	224,746,000	241,225,000	227,190,000 7/
1995	233,522,000	244,745,000	240,316,000	217,929,000 8/9/
1996	230,256,000	233,890,000	231,865,000	233,890,000 8/
1997	226,913,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ Excludes enacted administrative reduction of \$519,000.

4/ Excludes enacted administrative reductions of \$2,924,000.

5/ Excludes enacted administrative reductions of \$1,459,000, and enacted rescission of \$258,000.

6/ Excludes enacted administrative reductions of \$2,438,000.

7/ Excludes an enacted administrative reduction of -\$6,415,000.

8/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

9/ Excludes enacted administrative reductions of \$438,000.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Detail of Full-Time Equivalent Employment (FTE)

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Office of Director 1/.....	749	657	657

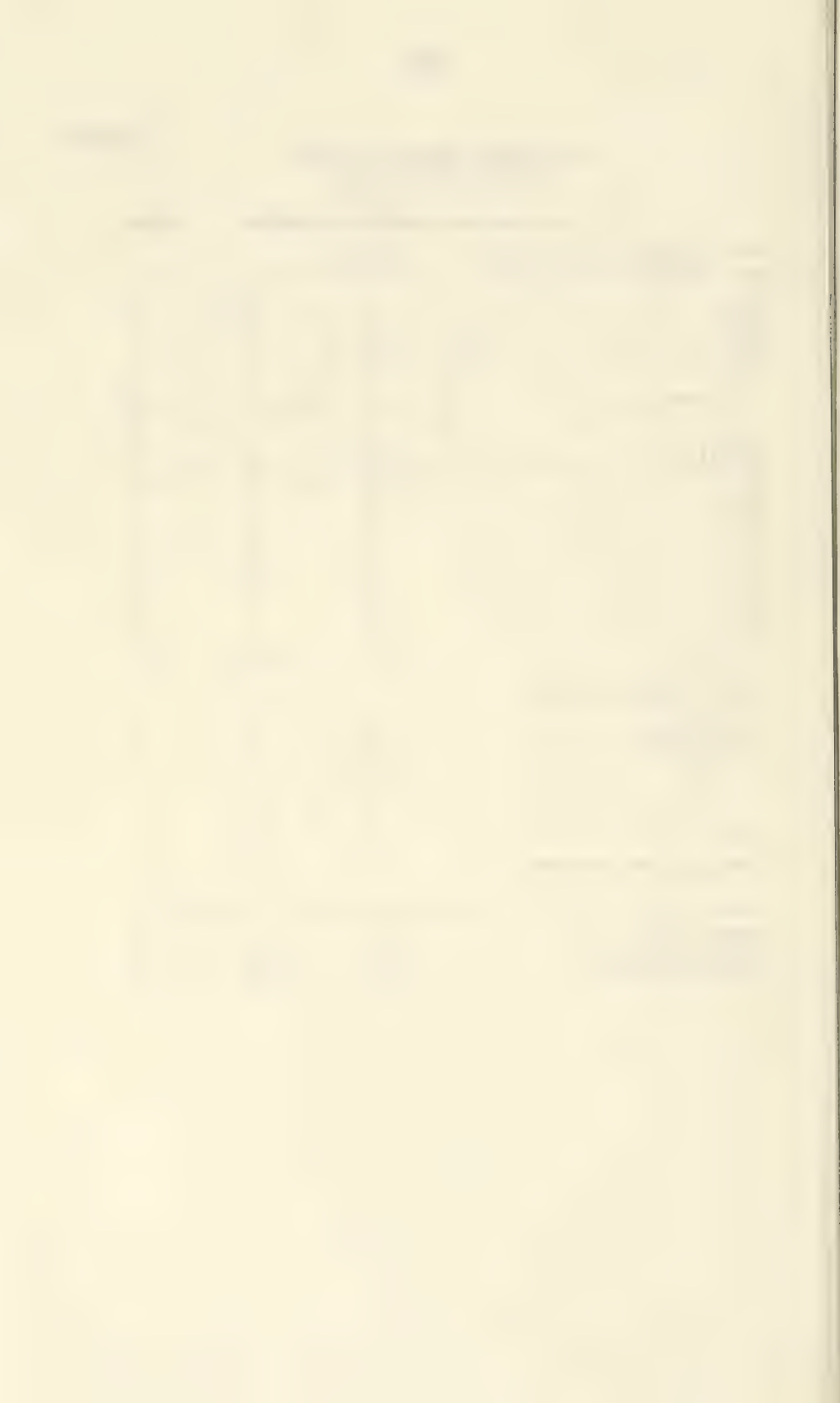
Average GS/GM Grade

1992.....	10
1993.....	10
1994.....	11
1995.....	11
1996.....	11
1997.....	11

1/ Includes 65 FTEs in FY 1995, 51 FTE's in FY 1996 and 51 FTEs in FY 1997 associated with AIDS Research Activities.

DHHS - NATIONAL INSTITUTES OF HEALTH
Detail of End-of-Year Employment
Office of the Director

	<u>1995</u> <u>Actual</u>	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>
Executive level IV.....	1	1	1
Total - Exec. Lev. Sal.....	148,400	152,000	156,500
ES-6.....	1	1	1
ES-5.....	5	5	5
ES-4.....	4	3	3
ES-3.....	1	1	1
ES-2.....	1	1	1
ES-1.....	<u>5</u>	<u>5</u>	<u>5</u>
Subtotal.....	17	16	16
Total - ES Salary.....	1,804,800	1,731,500	1,783,500
GS/GM-15.....	55	48	48
GS/GM-14.....	24	73	73
GS/GM-13.....	131	114	114
GS-12.....	105	92	92
GS-11.....	44	38	38
GS-10.....	9	8	8
GS-9.....	58	51	51
GS-8.....	32	28	28
GS-7.....	90	78	78
GS-6.....	34	30	30
GS-5.....	20	17	17
GS-4.....	38	33	33
GS-3.....	5	4	4
GS-2.....	4	4	4
GS-1.....	<u>1</u>	<u>1</u>	<u>1</u>
Subtotal	710	619	619
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade.....	18	18	18
Senior Grade.....	2	2	2
Full Grade.....	<u>1</u>	<u>1</u>	<u>1</u>
Subtotal	21	21	21
Total permanent positions.....	749	657	657
Total positions, end-of-year.....	749	657	657
Total full-time equivalent (FTE) employment, end of year.....	749	657	657
Average ES level.....	5	5	5
Average ES salary.....	105,944	108,635	111,079
Average GS/GM grade.....	11	11	11
Average GS/GM salary.....	45,890	47,055	48,114



FRIDAY, APRIL 26, 1996.

**NATIONAL INSTITUTE OF ARTHRITIS AND
MUSCULOSKELETAL AND SKIN DISEASES**

NATIONAL INSTITUTE ON AGING

NATIONAL INSTITUTE OF DENTAL RESEARCH

NATIONAL INSTITUTE OF NURSING RESEARCH

WITNESSES

**DR. HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF
HEALTH**

**DR. STEPHEN I. KATZ, M.D., DIRECTOR, NATIONAL INSTITUTE OF AR-
THRITIS AND MUSCULOSKELETAL AND SKIN DISEASES**

**DR. RICHARD J. HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON
AGING**

**DR. HAROLD C. SLAVKIN, DIRECTOR, NATIONAL INSTITUTE OF DEN-
TAL RESEARCH**

**DR. PATRICIA A. GRADY, DIRECTOR, NATIONAL INSTITUTE OF NURS-
ING RESEARCH**

**DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY FOR BUDGET,
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

INTRODUCTION OF WITNESSES

Mr. PORTER. Today is our last NIH hearing for this fiscal year. We're returning this morning to the panel format we experimented with on Monday. We will hear this morning from Dr. Stephen Katz, the Director of the National Institute of Arthritis and Musculo-skeletal and Skin Diseases, Dr. Richard Hodes, the Director of the National Institute on Aging, Dr. Harold Slavkin, the Director of the National Institute of Dental Research, and Dr. Patricia Grady, the Director of the National Institute of Nursing Research.

We will hear about the commonalities in the research missions of these institutes. But I notice they have another commonality as well. Three of the four directors are making their first official appearance before this subcommittee in their current capacity. Drs. Grady, Katz and Slavkin, a special welcome to all of you today, as well as a welcome to Dr. Hodes, and of course, Dr. Varmus.

Dr. Varmus, would you like to begin with introductory remarks, and then we'll have a short statement from each panel member and then go to questions?

PANEL OPENING STATEMENT

Dr. VARMUS. Thank you, Mr. Porter. I'd like to say one or two words.

As you pointed out, this is our second experiment with a sci-entific panel. Today, rather than have a single rubric for this

group, such as neuroscience, we have four institutes represented that address a wide variety of illnesses. These illnesses are particularly complex in their manifestations. They present unusual challenges to our scientific abilities. And in general, they require an intensity of medical care.

They are chronic, they are costly, they are crippling. They affect all of us in one way or another, and they frequently are associated with aging. They require that these institutes collaborate with each other in twos or threes or fours and coordinate their activities in ways that I hope we'll be able to discuss with you during the course of this hearing.

Thank you.

Mr. PORTER. Dr. Katz, then we'll go right across.

NIAMS OPENING STATEMENT

Dr. KATZ. Thank you very much, and good morning.

It's an honor for me to appear before this committee. I bring a perspective of almost completing my first year on the job, and it has been an exciting one. The NIAMS Institute has a broad mandate that includes arthritic, musculoskeletal, and skin diseases. Whether the research is in the basic area, animal models, clinical or prevention, our goal is to improve the lives of patients and to prevent disease in others.

AUTOIMMUNE DISEASES

I'd like to share highlights of achievements and plans in three areas. Those three areas are autoimmunity, diseases of bone, and some of the studies from our intramural research program. Autoimmune diseases are characterized by the body attacking itself, sometimes in organ specific areas and sometimes throughout the body in many organ systems. Autoimmunity underlies many of the research areas of the Institute. Some examples, include: rheumatoid arthritis, Sjogren's Syndrome, psoriasis, vitiligo, scleroderma, many blistering skin diseases, and lupus erythematosus. Many of these diseases disproportionately affect women and minorities.

SYSTEMIC LUPUS ERYTHEMATOSUS

I'd like to share some exciting new findings in lupus erythematosus. One is in the area of genetic risk factors. It's been shown very recently that in African-Americans, lupus kidney disease is associated with an abnormal receptor on a cell. Normally, receptors on cells help clear out immune complexes that are in the circulation.

If one has an abnormal cell surface receptor, as occurs in African-Americans with lupus kidney disease, immune complexes are not removed from the circulation, deposit in the kidney and thereby produce the disease. The potential of these findings is to enhance our understanding of the genetics of lupus and also to potentially lead to new therapeutic interventions.

Another exciting clinical initiative is our support of a multi-center clinical study of the use of estrogens in patients with lupus erythematosus. Usually, patients with lupus are told not to take es-

trogen because it worsens the disease. That is thought by some, but clearly not by all.

This study will tell us if estrogen use is safe, and thereby afford patients an alternative contraceptive in childbearing years and also hormone replacement therapy in post-menopausal women. The co-sponsors of these studies are the Office of Research in Women's Health and the Office of Research in Minority Health.

In all autoimmune disease, basic and clinical research are critical to our understanding. Advances in one of these areas provides potential insights in the underlying mechanisms of other diseases. In the area of bone disease, the second area, osteoarthritis and osteoporosis are clearly the most prevalent. I'd like to focus my comments on osteoporosis.

OSTEOPOROSIS

Osteoporosis affects 25 million Americans. Women are affected four times more commonly than men. Osteoporosis is thinning of bone. It results in fractures of the hip, the spine and the wrist. Here again, basic and animal models and treatment and prevention studies are what the Institute is supporting.

In the area of prevention, it is most important to identify patients at risk. This year, there were two studies supported by NIAMS that demonstrated a new technology, quantitative ultrasound, which is rapid, inexpensive and radiation free. The findings using quantitative ultrasound correlate well with who is at risk for fracture occurrence.

Other clinical studies in osteoporosis that the Institute is supporting are studies in calcium intake in young women to determine whether bone density can increase when women are in their 20s and 30s. Another study is in the area of slow release fluorides, to determine whether slow release fluoride, a new composition, can effectively prevent fractures of the spine in women.

Numerous collaborations occur within the institutes and within other Federal agencies. We chair a Federal Working Group on Bone Diseases, which is comprised of 11 institutes and 6 other Federal agencies. As well, we have developed the National Osteoporosis Data Group. These collaborations result in cooperative studies between various institutes and centers.

INTRAMURAL RESEARCH

The third area I want to talk about is the intramural research program, in which we are studying fundamental aspects of cell signaling. That is, how does a cell know from the outside what it should be doing on the inside, how is that information transmitted? This is a general, basic biological question that's being asked using lymphocytes and other cells of the immune system. Scientists have discovered a novel enzyme JAK3, that is actually activated by signals from outside the cell. This work has been translated to the study of patients, so we know now that some children have genetic defects in the DNA encoding this enzyme, and these patients have immunodeficiency diseases.

In addition to these areas I have described, the NIAMS supports research that has resulted in many other exciting advances, and we have identified significant scientific opportunities to pursue in the

next year. Diseases within the purview of NIAMS, as Dr. Varmus said, are chronic, common, crippling, costly and compromise the lives of many Americans. We plan to continue to support research that improves the quality of life for patients and their families.

FY 1997 BUDGET REQUEST

The budget request for fiscal year 1997 is \$243,169,000. I would be pleased to answer any questions.

Thank you.

Mr. PORTER. Thank you, Dr. Katz.

[The prepared statement and biography of Dr. Stephen Katz follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases

It is an honor for me to appear before this Committee as the new Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. I bring the perspective of almost completing my first year on the job, and I am pleased to report that it has been an extraordinary year for me and for the Institute. I am delighted to share with you some highlights of achievements and plans we have for scientific research in the areas of arthritis and musculoskeletal and skin diseases.

Striking advances in genetics have dramatically improved the pace of research to identify the genes that contribute to lupus susceptibility, severity, and mortality. On March 1, 1996, scientists reported the identification of a genetic risk factor for lupus kidney disease in African Americans. Lupus is one example of the many diseases within the research mission of NIAMS that affect women and minorities disproportionately. To address this, we interact closely with our colleagues in the Office of Research on Women's Health and the Office of Minority Health. An example of this interaction is our co-funding of the first clinical trial on the safety of estrogens for women with systemic lupus erythematosus. Currently, women with lupus are usually advised not to take any medications with estrogen in the belief that it will worsen their disease or cause problems with blood clotting. We are supporting this study because women with lupus now have limited options for contraception during child bearing years and for hormone replacement therapy during postmenopausal years. The outcomes of this trial are expected to have a significant effect on treatment options, health, and quality of life for patients with lupus. The NIAMS has also established a registry for patients with lupus as well as a repository for genetic material from patients and their families to enable the identification of the genes involved in susceptibility to lupus erythematosus.

Fibromyalgia is another multisystem disease that affects women far more commonly than men. The disease is characterized by low pain thresholds at specific tender points in the body. Using a new imaging technique, investigators recently determined that blood flow to particular parts of the brain was reduced in women with fibromyalgia. This suggests that structures in the brain involved in pain perception may have a functional abnormality that accounts in part for the lower pain thresholds. To address the clinical challenges presented by patients with fibromyalgia, the NIAMS is actively collaborating with other Institutes, fibromyalgia researchers, neuroscientists, endocrinologists, and other investigators from throughout the country on a workshop planned for the summer of 1996. The goals of this workshop are to assess progress in our understanding of fibromyalgia, to identify new directions in research on fibromyalgia, and to stimulate increased interest in this field.

Many of the diseases under the purview of the NIAMS are thought to be caused by autoimmune mechanisms. This phenomenon is a real tragedy of nature--when the

body actually turns against itself and fights its own cells and tissues. The results can be devastating for patients afflicted, resulting in rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and many skin diseases, for example. A key research priority for our Institute is to understand what causes the body to tolerate its various tissues in normal circumstances and what triggers it to reject its own tissues and cause these autoimmune diseases. A better understanding of the causes of these diseases can be expected to lead to the development of improved and more specific therapies that are less toxic for patients.

Osteoporosis, the most prevalent bone disease that afflicts Americans, is characterized by thinned bones that result in bone fragility and an increased risk of fractures. The major fracture sites associated with osteoporosis are the hip, spine, and wrist. Research in this area runs the full spectrum from basic to animal models to clinical to prevention studies. The basic bone biology initiative was created jointly by NIAMS, NIA, and NIDDK with the goal of encouraging and supporting new basic research in the areas of bone structure, formation, remodeling, and repair. Powerful animal models have already provided vital information. Clinical studies on osteoporosis include treatment of calcium deficiency in young women, fluoride effects on fracture rate, genetics and bone density, and the role of tamoxifen in bone loss and remodeling. In prevention, the identification of people at high risk for fracture before a fracture occurs is a major goal of research in this area. A valuable technology is now available for patients with osteoporosis. Several large prospective studies reported this year have indicated the utility of ultrasound measures in predicting fractures. Ultrasound technology offers a rapid, inexpensive, and radiation-free alternative to other measures of bone mineral density for the assessment of osteoporosis. Collaborative groups such as the Federal Working Group on Bone Diseases and the National Osteoporosis Data Group help to coordinate research on bone diseases and ensure effective utilization of our resources.

Osteoarthritis is the most prevalent acquired connective tissue disorder that affects the joints. Osteoarthritis and rheumatoid arthritis are major contributors to disability in the American public. As our population ages, the toll these diseases take on quality of life can be expected to increase significantly. In these forms of arthritis there is a breakdown of cartilage. The NIAMS continues to support studies of how and why cartilage-producing cells are injured and how we can better promote growth of these cells. In addition, numerous studies are attempting to understand and reverse the enzyme-induced breakdown of cartilage tissue.

Various forms of arthritis as well as osteoporosis often lead to severe pain, immobility or fracture of the hip. Total hip replacements transform quality of life and productivity as they enable people to walk who were once disabled by joint disease or fracture. The NIAMS sponsored a workshop on total hip replacement, and we launched a biomaterials research initiative to focus on extending the survival of artificial joints. Current studies are addressing the reasons for implant failure and are attempting to modify the artificial joints to adhere better to bone.

Another example of the strong interaction across the Institutes, as well as a common theme throughout NIAMS-supported research, is the new NIH initiative on bone and connective tissue repair. The repair of bone and connective tissue after damage from injury or degenerative disease is a long-standing research problem, and we have partnered with the National Institute of Dental Research to support research in this area. These studies will increase our understanding of osteoporosis, wounds of skin and oral tissues, joint damage in osteoarthritis, and injuries to muscles, tendons, and ligaments.

The American work place has changed significantly, and there has been a concomitant change in the disorders affecting American workers, such as low back pain and repetitive motion injuries. Low back pain affects an estimated 70 to 85 percent of Americans at some time in their lives. The NIAMS is initiating a clinical study on low back pain under acute conditions. This will fill an important gap in this field, as much of the present research base deals with chronic low back pain, and less is known about acute low back pain. With regard to repetitive motion injuries, the national rate of reported cases has increased dramatically and it has a significant impact on American industries and businesses. The NIAMS co-sponsored a workshop with the National Center for Medical Rehabilitation Research of the NICHD, and the American Academy of Orthopaedic Surgeons. Clinicians, scientists, and ergonomists met to identify research opportunities that the NIAMS is exploring such as the pathophysiology, diagnostic criteria, therapy, rehabilitation, and prevention of repetitive motion disorders.

Another underlying theme for research that the NIAMS supports is genetics. A major area of focus for the NIAMS over the coming years will be the identification of genes involved in diseases, both those caused by a single gene defect, as well as those in which multiple genes are involved. The importance of this focus is very apparent in the stories of research on the skin. Research on normal and diseased skin has profited tremendously from the advances in genetics, including hereditary blistering skin disorders such as epidermolysis bullosa. Scientists have now characterized many of the proteins of the skin basement membrane zone and cloned many of the genes involved. As the genetic origins are revealed, a renewed optimism has been generated for altering the course and for improving treatments for these diseases.

Another skin disease, psoriasis, affects several million Americans. It is a chronic and sometimes life-long disease with a strong hereditary component. The NIAMS and the National Psoriasis Foundation have sponsored several research workshops on this disease, resulting in the establishment of a national tissue bank where skin and blood samples are collected from patients with various forms of the disease. Research using tissues from this bank has resulted in the identification of a gene on a specific chromosome in some forms of psoriasis. Other research indicates that multiple genes are involved in this disease process. Once all the specific genes have been identified and their products determined, greater insights will be revealed on the disease process involved in psoriasis and intervention and treatment can be improved.

Scientists in the NIAMS intramural program have discovered a new enzyme (JAK3) involved in regulating white blood cell growth and development. Defects in the JAK3 enzyme were recently found to be responsible for severe immunodeficiencies in some children. These findings suggest that this enzyme may be a good target for designing drugs that could be used to treat autoimmune disease and transplantation rejection.

In addition to our mandate to support science of the highest quality, we also have a responsibility to ensure that results of our research are disseminated to clinicians and patients. We have pursued a number of avenues to make our research findings available. When the state of the science is ready, we have supported Consensus Development Conferences to bring a focus on a particular area of research. We are also supporting an Osteoporosis and Related Bone Disease--National Resource Center. The purpose of this Center is to expand awareness and enhance knowledge and understanding of the prevention, early detection, and treatment of osteoporosis and related bone diseases; and to broaden the knowledge base to enhance primary prevention of osteoporosis and reduce its consequences. Through these mechanisms, the NIAMS is working to ensure that all Americans have access to the latest research results.

This is a very exciting time to be a part of the NIH as positive changes are emerging. We look forward to the completion of the Clinical Research Center on the NIH campus. The diseases in our research areas lend themselves very well to full utilization of the services this new Center will offer. Our intramural program has a large clinical component, and it is essential that we have access to patients to carry out translational research. Many critically important, long term studies are possible only in the type of setting offered at the Clinical Research Center as a substantial investment of time and resources are required. An excellent example of this is the studies done over ten years in the NIH Clinical Center that determined the effectiveness of cyclophosphamide as an adjunct to corticosteroid therapy for the treatment of kidney disease in lupus erythematosus. These were key studies that, in fact, changed the clinical treatment of patients with lupus erythematosus. In addition, valuable material from patients involved in Clinical Center studies is often able to be used in other research studies elsewhere. I am confident that the new Clinical Research Center will serve as an invaluable resource for researchers on the NIH campus as well as those around the world. The NIH is a unique national and international entity--a place where seminal basic studies yield results that are applied daily to challenging clinical problems. Ours is truly a bench to bedside endeavor.

To carry out our mandate more efficiently, the NIAMS has undertaken many steps to streamline our programs and our administrative procedures. As the new Director of the NIAMS, I have undertaken a comprehensive analysis and evaluation of every program in the Institute. As we are constantly called to set priorities, we must ensure that we are using our resources to address the most compelling research needs, to identify critical gaps in our knowledge, and to explore scientific opportunities in order to understand and conquer the many diseases affecting the American public. Within the

purview of the NIAMS are included chronic, crippling, common, and costly diseases that compromise the lives of Americans, and collectively diminish our national economy in health care costs and lost productivity.

I am excited about the research we are supporting. It will improve our ability to understand, diagnose, treat, and ultimately prevent the challenging diseases in our research mission, diseases that touch every age and population group in America. We are firmly committed to reducing the costs of these diseases, both in economic measures and, more significantly, in the toll they take on the physical and emotional health of Americans. Our goal is to continue to support research that improves the quality of life for affected patients and their families.

The budget request for the NIAMS for Fiscal Year 1997 is \$243,169,000. I would be pleased to answer any questions that you might have.

Stephen I. Katz, M.D., Ph.D.

Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Date and Place of Birth: January 26, 1941; Brooklyn, New York

Citizenship: United States

Marital Status: Married, three children

Education:

1962	B.A., University of Maryland, (with Honors)
1966	M.D., Tulane Univ. Medical School, (with Honors)
1974	Ph.D., (Immunology) University of London

Professional History:

1966-1967	Medical Internship, Los Angeles County Hospital, California
1967-1970	Dermatology Resident, University of Miami School of Medicine, Florida
1970-1972	Major, U.S. Army, Walter Reed Army Medical Center, Washington, D.C.
1972-1974	Research Fellow, Department of Pathology, Royal College of Surgeons of England, London, England
1974-1977	Senior Investigator (Dermatology), Dermatology Branch, NCI, NIH
1977-1980	Acting Chief, Dermatology Branch, NCI, NIH
1980-present	Chief, Dermatology Branch, NCI, NIH
1989-1995	Marion B. Sulzberger Professor of Dermatology, Uniformed Services University of the Health Sciences (USUHS), Bethesda, Maryland
1993-1995	Acting Chairman, Dermatology Dept., USUHS
1995-present	Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

Professional Organizations:

Society for Investigative Dermatology, (President, 1993-94); American Academy of Dermatology, 1971-present; American Board of Dermatology, 1988-1995; Association of Professors of Dermatology, 1988-present; Clinical Immunology Society, (Secretary-Treasurer, 1991-1995); International Committee for Dermatology, (Secretary-General, 18th World Congress of Dermatology, 1992).

Editorial Boards:

Proceedings of the Association of American Physicians, 1995-present; Medicine, 1992- present; Archives for Dermatological Research, 1986-present; Journal of Dermatological Sciences, 1989-present; Experimental Dermatology, 1990-present.

Honors, Awards:

William Montagna Award of the Society for Investigative Dermatology, 1981; Superior Service Award of the Public Health Service, 1981; First Annual Marion B. Sulzberger Professor of the Year Award given by the American Academy of Dermatology, 1984; Distinguished Service Award of the U.S. Public Health Services, 1985; NIH Director's Award, 1989; Election into Institute of Medicine of the National Academy of Sciences, 1992; Presidential Executive Meritorious Rank Award, U.S. Government, 1994; Distinguished Service Medal, Uniformed Services University of the Health Sciences, 1996; D. Martin Carter Mentor Award from the American Skin Association, 1996; Outstanding Alumnus Award of Tulane University Medical School, 1996.

Mr. PORTER. Dr. Hodes?

NIA OPENING STATEMENT

Dr. HODES. Thank you, Mr. Chairman.

I appreciate the opportunity to discuss with you an overview of the scientific research programs supported by the National Institute on Aging. The importance and impact of aging research is demonstrated by the dramatic changes which are occurring in the age profile of the American population. As you can see in the first poster, the number of Americans over age 85 as recently as 1960 was less than 1 million. By 1980, this had doubled to 2 million. And conservative estimates are that by the year 2000, this will reach 4 million, by the year 2020, 7 million, and by the year 2040, 14 million Americans over the age of 85.

This change makes imperative the mission of the National Institute on Aging to support basic research in the nature of normal aging and to understand the conditions and diseases that affect older people in order to promote more disease-free and independent life for the increasingly long-lived American population. Accomplishments over the past year provide witness to the ability of research, biomedical and behavioral research, to meet this challenge.

ALZHEIMER'S DISEASE

The potential demographic implications of the changes in American aging are illustrated in the example of Alzheimer's disease. Approximately 3 percent of individuals age 65 to 74 are affected by Alzheimer's disease. By age 85 and over, 47 percent, nearly half, are affected. If there were to be no increase in this relative incidence of Alzheimer's disease over the next 40 years, the number of people affected will increase several fold, beyond the 4 million currently afflicted, with a corresponding increase in cost and human suffering.

The most fundamental and dramatic changes in the understanding of Alzheimer's disease over the past years have included the demonstration of strong genetic risk factors for the disease. Research in this area has proceeded and continues to proceed at a dramatic and accelerating pace.

Over the past five years, four separate genes have been identified as risk factors for Alzheimer's disease, the last two of these being discovered in the last two months. Three of these genes located on chromosomes 1, 14 and 21 are associated with particularly aggressive early onset forms of familial Alzheimer's disease. The more common late onset form of Alzheimer's has been associated with variants in the apolipoprotein, or ApoE gene, on chromosome 19.

The demonstration of these genetic risk factors has now driven a body of research aimed at understanding the mechanisms by which the associations between these genes and disease occur. There have been animals generated in which genes such as ApoE have been knocked out. Transgenic mice in which the abnormal amyloid genes associated with certain forms of familial Alzheimer's were introduced, have provided, for the first time, an animal model or animal models in which researchers can study Alzheimer's disease.

If it should be demonstrated that ApoE, amyloid, or the products of any of these Alzheimer's associated genes, are directly involved in the cause of Alzheimer's, they will provide opportunities and targets for intervention, for diagnosis, for treatment and ultimately for prevention of disease. It's critical that these cutting edge breakthroughs in biological sciences be translated into clinical applications.

One area in which this has been accomplished is in the area of diagnosis. Over the past year research supported by the NIA has demonstrated that genetic typing, together with new techniques in brain imaging, are capable of identifying abnormalities in brain metabolism in individuals at high risk for Alzheimer's disease up to 20 years before any symptoms appear. This provides opportunities for designing interventions at a time early in the stage of the disease before symptoms appear and before potentially irreversible changes in the brain have occurred.

In addition, NIA is supporting novel approaches to the therapy of Alzheimer's disease, with four clinical trials currently being supported, and the results from the first of these anticipated in the next few months.

BASIC AGING

An understanding of the basic process of aging is critical to understanding and optimizing human aging. One dramatic discovery reported last week, which received a great deal of media attention, was the identification of a gene associated with a rare disease known as Werner's Syndrome. Individuals afflicted with Werner's Syndrome have manifestations of early aging by the time they reach their 30s, having visible changes in hair and skin, as well as accelerated development of age-associated diseases, such as cardiovascular disease, diabetes and cancer.

It has now been demonstrated that the gene which is associated with this disease is what is known as a helicase. Helicases are enzymes which are important in unwinding DNA, a function critical to cell replication and to DNA repair. Studies such as these will drive further advances in our understanding of the basic processes underlying normal and abnormal aging.

DEMOGRAPHICS OF AGING

Finally, the question must be posed whether the demographic changes associated with an aging population carry with them an unavoidable increase in disability. There is evidence that this need not be inevitable. There has been a good deal of press attention in the past month reporting stories based on data illustrated in this chart, which indicate that, in fact, the rates of disability in older Americans have decreased over the past years.

The upper line on the chart indicates the number of Americans age 65 and over expected to have disabilities based on the rates of disability observed in 1982. The lower line represents the actual observation. The difference between these two lines corresponds to 1 million fewer Americans with chronic disabilities than would have been expected if the rates of disability had not changed since 1982.

Our ability to make increased improvements in prevention of disability is illustrated by results published in the past year as a result of NIA reported studies which demonstrate the ability of investigators to identify risk factors for falls in older people, and to design successful interventions to reduce rates of falls by 44 percent. These were demonstrated to be highly cost effective interventions by virtue of their prevention of injury and disability.

The challenge for the National Institute on Aging is to continue to accelerate progress in these areas. The fiscal year 1997 budget request for the National Institute on Aging is \$461,541,000. I would be happy to answer questions.

Thank you.

Mr. PORTER. We've never had anybody express it that exactly, Dr. Hodes. [Laughter.]

[The prepared statement and biography of Dr. Richard Hodes follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Aging

Mr. Chairman, we have all witnessed differences in how we age; some persons lead healthy, independent, and productive lives well into their 70's, 80's, 90's and even beyond; other persons succumb to age-associated diseases and disabilities in their 60's or even earlier. The National Institute on Aging (NIA) promotes research to understand the mechanisms of normal aging and their relationship to costly age-associated disease and disability. Each day we translate this new knowledge into strategies to improve the health and quality of life for older Americans.

The projected dramatic increase in the numbers of older persons is driving a growing interest in aging research. People over age 65, who constitute approximately 12 percent of the U.S. population now, will make up about 20 percent by the year 2025. In most industrialized countries, the 85 and older age group is the fastest growing segment of the older population. We face a growing public health and economic crisis unless we can prevent or slow the process of disease and disability among the elderly and develop more effective methods of care. NIA-supported researchers have made significant progress this year in our understanding of Alzheimer's disease (AD) and the basic biological processes that affect aging, as well as with new strategies to reduce the risk of physical disability. I would like to highlight for you some of the progress made in these areas.

AD is one of the most common causes of loss of mental function among people aged 65 and older. The tragic course of AD can range from 2 to 20 years. It proceeds in stages, gradually destroying memory, reason, judgment, language, and eventually the ability to carry out even the simplest tasks. There are an estimated four million Americans currently suffering from AD, and due to the projected growth of the older population, perhaps as many as 15 to 20 million will experience the devastating effects of AD in the early 21st century. The staggering economic burden of AD to families and society is currently estimated to be as high as \$100 billion per year.

In the past five years we have made remarkable progress in AD research. Scientists have discovered genetic mutations linked to AD on four separate chromosomes: 1, 14, 19, and 21. Chromosomes 1, 14, and 21 are associated with early-onset, familial AD, an aggressive form of the disease that can cause symptoms in people as young as 30 years of age. Scientists are now trying to discover precisely what abnormal proteins or processes these mutations generate and to clarify how these, together with environmental factors, play a role in the disease. Within the past five years, scientists discovered that the risk of developing the more common, late onset form of AD is linked to a gene located on chromosome 19 that codes for a protein known as ApoE. One of the variants of this gene, ApoE4, is associated with greatly increased susceptibility to AD and

earlier age of onset. In contrast, ApoE2 may confer a protective effect. These important discoveries have led to increased research activity to discover the molecular mechanisms underlying the effects of ApoE on the development of AD pathogenesis. If ApoE is directly involved in susceptibility for AD, it would then become a target for interventions.

The dual goals of accurate diagnosis and early detection have long been central to AD research. A recently reported study that combined the use of ApoE4 typing with brain imaging showed that it is possible to identify abnormalities in brain function of individuals who are at high risk for Alzheimer's disease, but who have no detectable disease symptoms, as many as 20 years before they would be expected to develop symptoms. This advance opens the opportunity for potential treatments which could be started before the brain has suffered damage from more advanced AD.

NIA-supported research on treatments for AD span a wide range of approaches, from research to develop candidate drugs to clinical trials of drugs that show promise. In addition to these efforts at drug development, research will continue on the effectiveness of behavioral approaches and services such as AD special care units, which are long-term care settings designed to meet the needs of people with AD and related cognitive impairments. The results of research on special care units should inform public policy on ways to improve care for Alzheimer's patients by determining the effectiveness of special care units for their residents, their families, and the unit staff members.

Parallel to the discoveries in basic neurobiology, which should eventually enable us to prevent nerve cell destruction and onset of Alzheimer's disease symptoms, research on the basic biology of aging will provide the foundation for developing new or improved interventions to combat multiple age-associated diseases and disabilities. Recent research has advanced our understanding of the genes and biochemical pathways involved in regulating the life span of some lower organisms. By incorporating these "longevity" genes into the chromosomes of experimental animals, NIA researchers have actually been able to increase life span. Once researchers have a better understanding of life span control in simple animals, they will be able to study life span control in more complex animals and determine the relationship of these processes to human aging, health and disease, and longevity.

Both aging and cancer researchers share interest in one particular field that concerns the end structures on chromosomes known as "telomeres," structures which serve to maintain the chromosome's integrity and stability. We now know that telomeres play a key role in determining the capacity of individual cells to divide; after losing this capacity, cells become senescent. Telomerase is an enzyme that works to maintain telomere length by compensating for the shortening which occurs each time the cell divides. Cancer cells express relatively high levels of telomerase which enables them to divide indefinitely. A more complete understanding of telomerase and telomere length regulation should lead directly to studies on the delay of cellular senescence and age-related disease, as well as to new strategies to prevent the unlimited replication of cancer cells.

Another important area in basic aging research is that of oxidative damage. Damage to cells and subcellular components from "free radicals," which are naturally occurring byproducts of normal metabolism, has long been believed to be a factor in the degenerative processes which accompany aging in all animal species. Recently completed research demonstrated a strong inverse correlation between life span and the level of free radicals produced by mitochondria, the energy-producing powerhouses located within all cells. Thus, a promising intervention against age-associated disease and disability might be one which would reduce the level of free radicals by increasing the biochemical efficiency within the cell's mitochondria.

The NIA also conducts research with immediate clinical significance. Physical disability is a major concern to older persons and is associated with billions of dollars spent annually on long-term care. For many older persons, physical disability is the result of multiple, complex, and interacting factors. Osteoporosis, which affects an estimated 25 million older Americans, most of them women, is an obvious example of a major risk factor for physical disability. Osteoporosis predisposes older persons to serious and debilitating fractures. Each year, thousands of older Americans, more women than men, are hospitalized and then admitted to costly long-care facilities because of hip fracture. Recent studies revealed that estrogen use is associated with lower hip fracture rates, indicating the potential for preventing bone loss and related fractures. Other researchers conducting a four-year longitudinal study of women identified hip fracture risk factors which allow targeting of very high-risk women for preventive strategies. There was a 25-fold difference in hip fracture rate between those women with two or fewer risk factors and normal bone density, and those women with five or more risk factors and low bone density. Maintaining body weight, walking for exercise, avoiding long-acting benzodiazepines, minimizing caffeine intake, treating impaired vision, and taking measures to maintain bone density are among the steps identified that may decrease hip fracture risk. NIA will continue to fund basic laboratory studies of the biology of osteoporosis and bone cell function, clinical studies of age-related bone loss and fracture epidemiology, and trials to prevent and reverse bone loss.

Menopause is a universal phenomenon in women and until recently has been understudied. To gather critical information on the chronology of the biological and psychosocial factors related to menopause and its subsequent effects on health and age-related disease, NIA supports the *Study of Women's Health Across the Nation (SWAN)*. This study will generate extensive data on menstrual cycle characteristics such as ovarian function, health and social characteristics, nutrition, ethnicity, reproductive history, risk factors for diabetes, hypertension and cardiovascular disease, and physical activity.

Falls and resultant injuries are a major cause of disability in older Americans. During the past year, NIA-funded researchers conducted the first randomized controlled trial using a multiple risk factor approach to reduce disabling falls in older people. Risk factors which were targeted by this study included bone fragility and muscle weakness, use of sedatives or multiple medications, impairments of motion such as balance and gait, and environmental hazards.

Participants received individualized treatment, including medication adjustments, strength and balance training, and instruction on safe practices to avoid lightheadedness and environmental hazards. Over a one-year follow-up period, the participants' rate of falls was reduced by nearly half compared to that of the control group. The intervention was also shown to be significantly cost effective, lowering the average annual cost of health care for individuals in the highest risk group by nearly \$3,700, even after factoring in the cost of the intervention. Since more than 250,000 hip fractures occur each year among older persons, a substantial cost savings should result from incorporating such a strategy into health care practices.

Cardiovascular disease is another major cause of disability and remains the leading cause of death of older Americans, killing approximately half of those age 65 and older. Although age is the main risk factor for cardiovascular disease, the precise reasons are presently unknown. One potential risk factor for cardiovascular disease in the elderly is stiffening of the large and medium-sized arteries, leading to increased stress on the heart. NIA is conducting research to identify ways of preventing and reversing vascular stiffening, such as exercise and other beneficial lifestyle changes. Other NIA researchers are evaluating the possible roles gene therapy may have for treatment of age-associated heart disease. These scientists are examining whether gene therapy can be used to enhance blood circulation in animal models of chronic heart disease and have successfully induced the growth of new coronary blood vessels in laboratory animals to reestablish blood flow following heart attack. In another study, gene therapy is being tested as a way to combat the renarrowing of blood vessels following angioplasty, a technique used to open narrowed coronary arteries. The potential benefit of preventing or reducing age-associated cardiovascular disease is considerable, both in terms of cost savings and quality of life of older Americans.

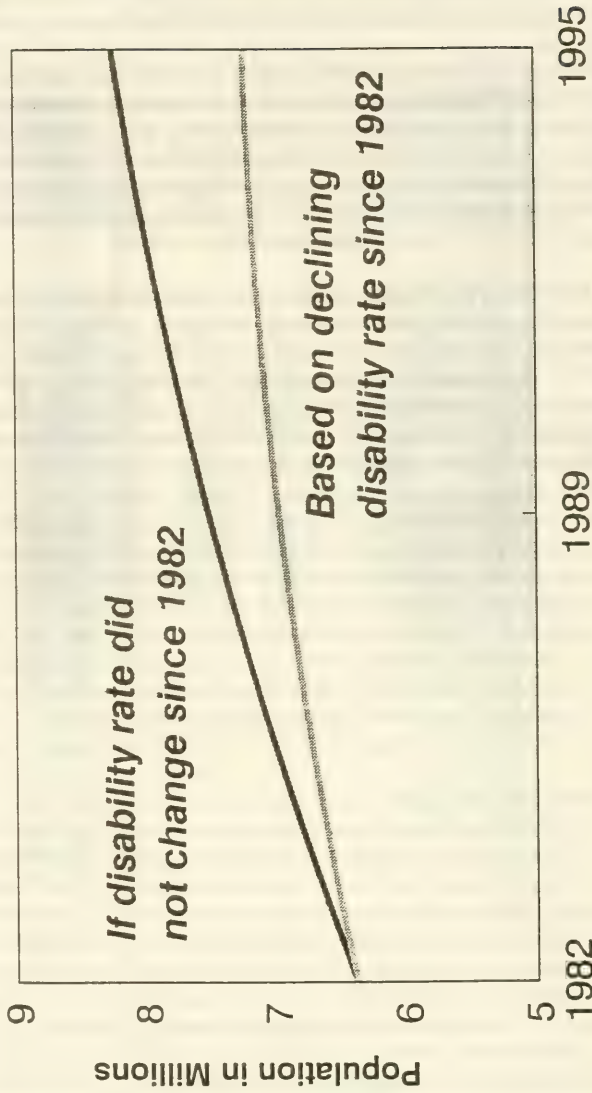
Many of the problems of aging result from behaviors that place individuals at greater risk for poor health, depression, and other negative outcomes. NIA-supported research has documented the benefits for health and longevity of adopting healthy lifestyle practices, such as physical activity and nutrition, and avoiding health-impairing habits, such as smoking, even at a very old age. As one example, numerous studies have documented the influence of exercise and physical activity on longevity, even among the oldest old. Recent studies also show the benefit of regular exercise in reducing costly hospital stays and nursing home admissions. Current research advances document the importance of the social and behavioral context when studying physical activity and exercise among older adults. Nevertheless, surveys report that older people often are not motivated to make the desired changes. Additional research is therefore being stimulated on topics such as the social and behavioral factors involved in initiating and maintaining health-enhancing behaviors, the role of health care providers in identifying risk and encouraging positive self-care practices, and the design of regimens appropriate for older people in community and institutional settings. Even with the hope of major advances in the treatment and prevention of disabling conditions, the demand for long-term care is expected to increase due to predictable demographic trends. Research will be conducted on many aspects of

long-term care, particularly on new and evolving forms of care with a goal of identifying the most effective and cost-efficient approaches.

As life span and vitality in later life have increased, more and more older people are able and willing to work productively well into late adulthood. According to NIA's Health and Retirement Survey, almost three-fourths of American workers now would prefer to phase in their retirement with a gradual shift to part-time work rather than stop working abruptly. One major goal of this research is to understand the productive potential represented by workers over age 60, especially for part-time engagement in the workforce.

A vision for 21st century America drives our research efforts. It is the prospect of an older but healthier population of productive and independent citizens. Mr. Chairman, in order to achieve this vision, the FY 1997 budget request for the National Institute on Aging is \$461,541,000. In making this request, the NIA recognizes its responsibility to remain responsible stewards of these funds. We have implemented and will continue to identify initiatives that maximize scientific and management efficiency. I would be happy to answer any questions.

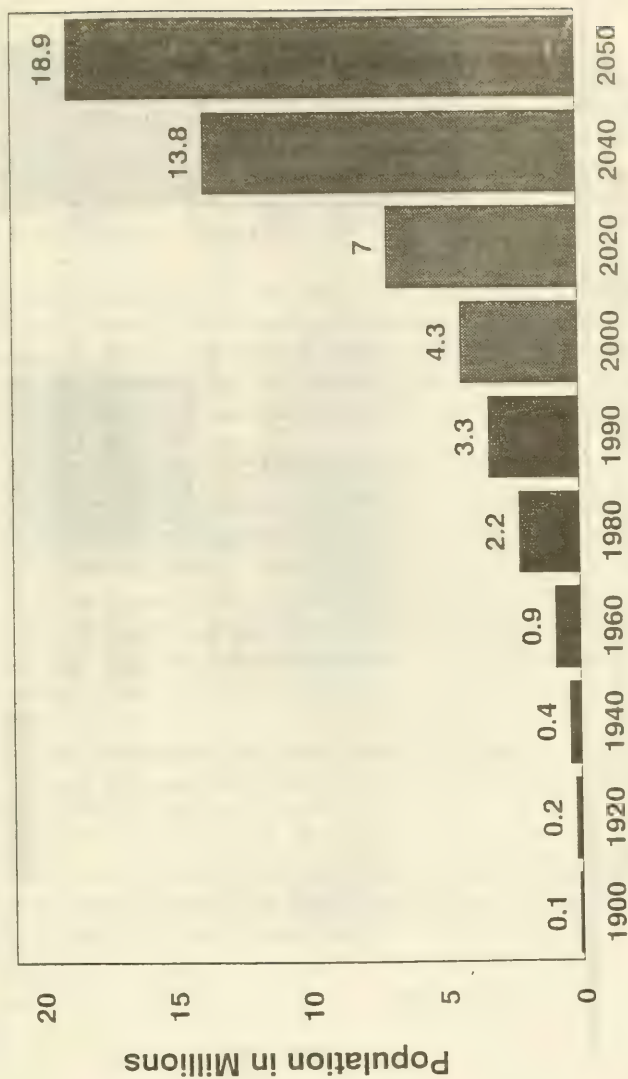
Projected vs. Actual Number of Chronically Disabled Americans 65 and Older



Source: National Long Term Care Survey 1982-1995

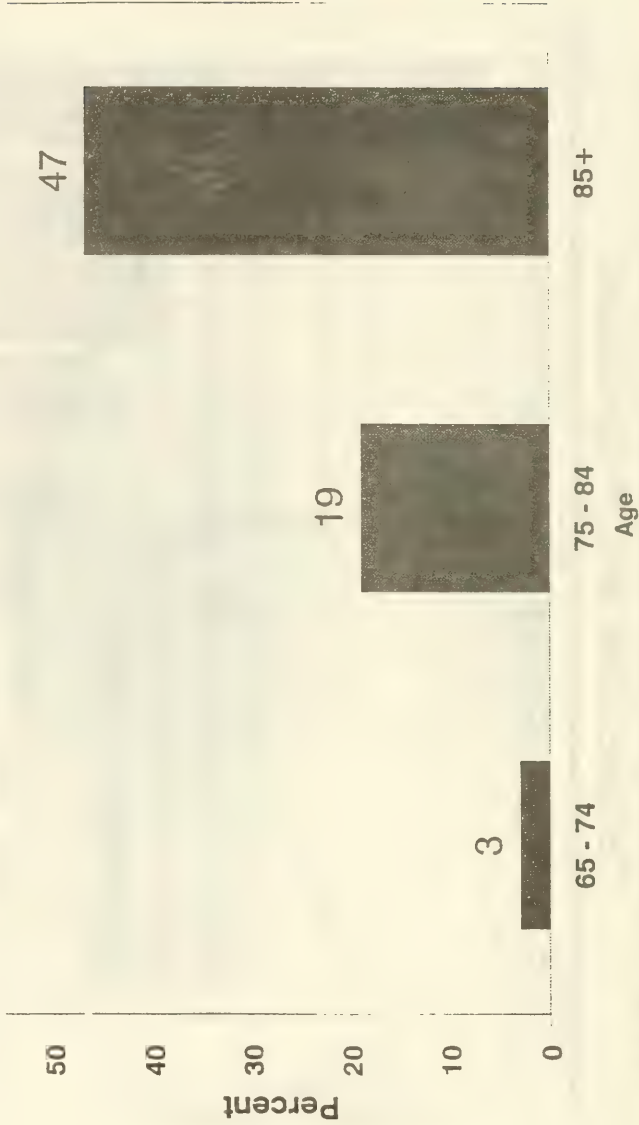
U.S. Population 85 and Older: 1900 - 2050

Census Data and Projections



Source: Bureau of the Census, *Current Population Reports*, P23-178RV (May 1993) and P25-1104 (Nov 1993)

Estimated Percentage of the Population 65 and Older with Probable Alzheimer's Disease



Note: Excludes people in nursing homes and other institutions.

Richard J. Hodes, M.D.

Director, National Institute on Aging

Dr. Richard J. Hodes, an eminent immunologist, directs the research program of the National Institute on Aging (NIA) at the National Institutes of Health (NIH). The NIA is the principal Federal funding agency for studies of the basic, clinical, epidemiological, and social aspects of aging. By promoting the continued development of a strong, diverse, and balanced research program at NIA, Dr. Hodes expects to fuel progress in aging research.

He maintains an active involvement in research on the NIH campus in Bethesda, Maryland, through his direction of the Immune Regulation Section, a laboratory devoted to studying regulation of the immune system, focused on cellular and molecular events that activate the immune response. This involvement in campus research also serves to strengthen ties with other NIH scientists involved in studies of age-related diseases.

Dr. Hodes was named Director of the NIA in 1993, but has enjoyed a long career in science at NIH, first as a clinical investigator in the National Cancer Institute, then as the Deputy Chief and Acting Chief of the Cancer Institute's Immunology Branch. Since 1982 he has served as Program Coordinator for the U.S.-Japan Cooperative Cancer Research Program, since 1992 on the scientific advisory board of the Cancer Research Institute, and since 1995 as a member of The Dana Alliance for Brain Initiatives.

He is an editor of several scholarly journals, including *The Journal of Experimental Medicine* and *Therapeutic Immunology*, and is a Diplomate of the American Board of Internal Medicine.

Dr. Hodes is a graduate of Yale University and received his M.D. from Harvard Medical School. As author of more than 190 research papers, he is an influential scientist and contributor to the field of immunology.

Mr. PORTER. Dr. Slavkin?

Dr. SLAVKIN. Good morning.

Mr. PORTER. Good morning.

NIDR OPENING STATEMENT

Dr. SLAVKIN. It's a pleasure to be with you. It's also been a pleasure to make the transition from being a citizen of a university to join the NIH, and to have the pleasure of working with Harold Varmus and my other new colleagues here in Washington.

In coming to a new environment, one of the discoveries that one needs to make rather quickly is to grasp all of the traditions that are excellent and need to be sustained, and to revisit the scientific portfolio and examine new opportunities, particularly scientific opportunities, that offer tremendous possibilities for the future. In terms of the National Institute of Dental Research, there is a long tradition of being able to move information from the bench to the community and in improving the quality of oral health of the American people. Over these last 48 years, the frequency of dental caries and the frequency of tooth loss and edentulism in the American people have been profoundly improved.

The calculations, which I believe you looked at last year, would indicate that the American people are saving approximately \$4 billion each year in their oral health bill. That savings turns out to be approximately double what the investment has been in the entire budget of the National Institute of Dental Research since it was created in 1948.

What I'd like to do is look to the future and indicate those scientific opportunities that we are currently working on in collaboration with other institutes as well as colleagues in universities around the country, with private industry, and when appropriate, with foundations that share an interest.

Every hour and 15 minutes in this country, a child is born with cleft lip and cleft palate. This translates into essentially an individual having the first 17 years of his or her life invested in a chronic, repeating treatment protocol that runs approximately \$100,000 per individual. Roughly \$1 billion is spent each year on the rehabilitation of young people who are born with facial clefting.

Now, of course, one of the opportunities is to discover what are the risk factors that lead to this type of deformity. In this country as well as in other parts of the world, in collaboration with studies in China and in eastern and western Europe, we are learning that there are a number of risk factors that can be translated in modifying human behavior to reduce the frequency of some of these birth defects.

In addition, 20 percent of these children are born with a genetic or inherited liability, and those genes are being discovered. The National Institute of Dental Research has supported a number of investigators who have isolated, characterized, cloned and then produced transgenic animal models, replicating the phenotype of cleft lip and cleft palate.

We're also interested in rarer disorders, disorders that happen with the frequency of one in 14,000 live births, such as Treacher-Collins syndrome. In February of this year, the gene for Treacher-Collins, called Treacle, was reported for the first time. This gene is located on chromosome 5.

That deformity is particularly interesting, because the Treacle gene is not only expressed in the formation of the mid-face and lower face, but it's also expressed in the central nervous system, and in heart, limb, and kidney development. These individuals often present syndromes, so genes found in one part of the body can be extremely informative toward solving problems in other parts of the body.

The second area that I'd like to share with you is that of chronic disabling disorders. And here, looking at the same individual, at 50 years of age and then at 75 years of age, the individual obviously presents the phenotype that my colleagues have just described. Those of us who look at the craniofacial-oral-dental implications of chronic disabling diseases are focusing particularly on the issues of chronic facial pain, including pain associated with the temporomandibular joint, the only moving joint in the head.

Approximately 7.5 million Americans have this disorder. And the humbling aspect is, we don't yet know how to make a differential diagnosis, how many different versions there might be of temporomandibular joint. Therefore, we're very interested in exploring the problems of what is the etiology, what is the pathogenesis, how to make precise diagnoses, how to measure these particular defects, and of course, how to come up with therapeutics that are appropriate, those therapeutics, not only for osteoarthritis and neuromuscular disorders, but also how to deal with long term chronic pain, how to work with new analgesics that have an affinity for binding to receptors that are excited and are the source of pain.

The third area that we are actively pursuing and we've had an opportunity to talk about this a little bit, is that essentially every hour in this country, an American is dying of nasopharyngeal, esophageal, or oral cancer. The risk factors are fairly well known, at least a few of them, tobacco products, alcohol products. After diagnosis and after treatment, the prognosis at the moment for Americans is approximately a 53-percent survival rate. So essentially, one out of every two individuals who are diagnosed eventually die of this disorder.

In collaboration with the National Cancer Institute and the American Cancer Society, through a number of oral health promotional activities, we are trying to reduce the risk factors in the American people. And we're trying to learn what are the genes involved or associated with these risk factors that manifest in changing a normal cell into a neoplastic cell. This also turns out to be a very, very interesting area for environmental insults, behavioral issues, and of course, the richness of cellular and molecular developmental biology applied to this area.

These are three areas—the birth defects, chronic disabling disorders, such as temporomandibular joint and chronic facial pain, and finally, oral cancer—that we're focusing on as we look at fiscal year 1997. I would like to present the budget for NIDR for fiscal year 1997. It is \$174,463,000.

Thank you very much.

Mr. PORTER. Thank you, Dr. Slavkin.

[The prepared statement and biography of Dr. Harold Slavkin follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Dental Research

This has been an extraordinarily rewarding year for biomedical science, for the NIH, and for myself personally. In July 1995 I left my laboratory at the University of Southern California to become the sixth Director of the NIDR, an organization established in 1948 to improve the oral health of all Americans. In the course of that half century we have seen biomedical research mature from a relatively primitive state to the discoveries of super genes and miracle molecules that make front page news in the Washington Post and the Wall Street Journal.

At the same time we Americans ourselves have matured. The baby boomers and their parents are grown up and older, tilting the compass of biomedical research increasingly toward chronic, disabling conditions. Unlike our grandparents however, we no longer accept the debilities of age. Indeed, debilities at any age are not to be tolerated. From the cradle to the grave we strive for good health and expect biomedical science to make it happen. Toward that end I want to spend the next few minutes describing three areas where NIDR is trying to do just that.

Let me begin with a subject that has been my special interest in research for 27 years--the development of the face, the teeth and all the attendant parts. I do not have to remind you how critical these features are: Our faces are our identity, they are how we see ourselves and others see us. Yet for many that identity has tragic beginnings. Three-fourths of all malformations seen at birth affect the head or the face or the neck. The most common of all is cleft lip or palate, which occurs in 1 out of 600 births. If you consider that there are 4 million births in America every year, that means that there is one baby born with a cleft every hour of every day of every year. For that child and that child's parents the years ahead will be spent in the care of a team of specialists: surgeons, pediatricians, dentists, speech therapists, social workers and others who will attend to the ever changing demands of growth and development that over a lifetime will cost over \$100,000.

The course is even more complex and costly for the hundreds of less common defects like this child with Treacher-Collins syndrome or this baby with Crouzon's. We now know the precise genetic error that leads to many of these syndromes. NIDR-supported scientists have discovered the genes responsible for Waardenburg syndrome, associated with eye and hair defects, for a condition of craniosynostosis in which skull bones fuse prematurely, applying pressure in the brain and deforming the face, and for some forms of cleft lip or palate. What is extraordinary is that often the error occurs at a single letter in the genetic "word" in question, and yet because that gene is one of the master genes that turns on early in development, it can have wide-ranging effects--not just altering the shape of the eyes or leading to the congenital absence of teeth, but causing heart or lung or gut defects, and even misshapen toes or fingertips. We are beginning to learn which master genes regulate the movements and destinies

of cells, and when and where those cells signal or receive critical information for the development of the face or teeth.

Basic research is revealing patterns of development that link us to the earliest forms of life on earth--flies and worms and fish--and these in turn have become important experimental models that explain how genes function; what happens in the absence of the gene--in so-called "knockout" animals when a gene has been eliminated in the embryo; and what causes genes to malfunction. We are translating that research into studies of the interactions between genetic, biobehavioral, and environmental factors in causing birth defects. Armed with this information, we can provide essential information to women who are pregnant or who want to become pregnant--pointing to the risks of drugs, certain medications, alcohol and cigarette smoking, as well as the importance of nutrients like folic acid. So we are moving to reduce the dismal statistics by promoting means of prevention. At the same time we are mastering the arts of diagnostic screening and detection; we are honing the skills of gene replacement that will some day lead to the ability to repair or correct genetic defects even before birth.

That kind of knowledge applies beyond the healing and repair of congenital anomalies. Every year millions of Americans are victims of accidents--on bicycles or skates, in cars or through falls and sports injuries, again, all too often resulting in trauma to the face and head. For them and for the countless millions who succumb to painful bone and joint diseases we need better solutions: ways to repair and replace tissues lost as a result of trauma or disease; ways to forestall the age-related changes that lead to stiff joints and fragile bones. And, while the Dental Institute can be justly proud that toothlessness has declined precipitously for the young and for the baby boomers, the latest survey of the National Center for Health Statistics indicates there are still close to 20 million adults who are missing all their teeth. Significantly, when I was born the human lifespan was 58 years; today Americans can anticipate living to be nearly 80. And as they are sure to tell you, today's generations of young and middle-aged expect to live those years with all their teeth and without walkers or wheelchairs.

The question then is how can we preserve our teeth and skeletons over the long haul? We believe the answer lies in a concerted effort in which NIDR and the other relevant NIH Institutes and Offices invest in collaborative research on the behavioral, environmental and biological aspects that work for or against a healthy old age. Basic science at NIDR has pioneered the discovery of the genes and proteins essential to teeth and bone formation. Our investigators are unravelling the intricate web of events by which bone- and tooth-forming cells secrete essential proteins into the surrounding cell matrix, where, in combination with circulating minerals, the body's hard tissues--bioceramics--are formed.

Of special importance in these studies has been the discovery of families of bone morphogenetic proteins (BMPs) and cartilage-derived morphogenetic proteins (CDMPs) that stimulate new bone and cartilage growth. Misspellings of the genes for some of these proteins have already been linked with a number of inherited bone diseases such as a form of dwarfism. And only this month it was reported in Nature Genetics that an error in yet another critical cell-surface molecule can lead to congenital malformations characterized by an overgrowth of tissue, skeletal manifestations, and cleft lip.

What these studies tell us is that at every stage of life, whether in development, in wound healing, or in aging, cells are in constant conversation with each other and the molecules in their neighborhood. Our research is geared to overhearing these conversations at the molecular level, understanding who the partners are, and learning how to interrupt when the conversation is imperfect or damaging. By so doing we are translating our cell biology and animal studies to clinical diagnostic tools and to the development of an entirely new approach to repair: one that uses the body's own growth factors and the body's own store of "stem" cells as resources. These are the parent cells that lie in bone marrow or tooth pulp, which, when stimulated, develop into bone- and tooth-forming cell lines. We are beginning to apply this research in animal and clinical studies that are now taking place on the campus at NIH in a bone clinic we have set up in the Clinical Center. In our first protocol we have extracted stem cells from patient volunteers and demonstrated that they can grow new bone when transplanted into mice. The next step will be to see if we can use these cells to build up the lower jaws of adults whose bones have resorbed because of missing teeth.

This kind of research is variously called tissue engineering or biomimetics--whatever the word it means repairing and regenerating body parts, not like the old TV \$6 million dollar man, but by following nature's own recipes.

Finally, we are taking a leaf from nature's book in the third initiative I want to describe to you today. In growth and development cells differentiate and divide and divide again as they form tissues and organs. The genes that govern these events follow a strict spatial and temporal schedule that proceeds in an orderly manner and then stops. Not so in cancer. There, the problem is uncontrolled growth and often the transformation of the cell to a more primitive, less differentiated form. Again the problem is genetic--genes that would normally suppress tumor growth may be mutated or lost for one reason or another; other genes that normally are quiescent may be turned on to stimulate cell division. The situation with regard to oral and throat cancers is particularly tragic: 30,000 adults are diagnosed with these cancers every year, more than cervical cancer, malignant melanoma, or Hodgkin's lymphoma. And each year 9,000 Americans die--one death every hour from oral cancer. The overall five year survival for both sexes and all races is 53%; for black males over 45, it is an abysmal 31 percent. And when oral cancer does not kill it leaves its stamp in the form of disfiguring surgery, pain, dry mouth, and often nerve dysfunctions that can affect speech, chewing, swallowing, and reduce taste perception.

Yet this cancer can be prevented. In my professional judgement, we need to invest in fundamental, environmental, and behavioral research. We know the major risk factors--tobacco products (smoking, chewing or spit tobacco) and alcohol and prolonged exposure to sunlight. Therefore, oral cancer is a classic example of a human disease which reflects the interaction of behavior, the environment, and molecular genetics. We need to understand the process of malignant transformation at the genetic and molecular level; we need to develop better diagnostic tests for early intervention, and we need to move on to so-called "smart" therapeutics--approaches which will not destroy healthy bone and salivary gland tissue adjacent to the cancer, but are aimed at replacing defective genes or inserting a "suicide" gene that will make malignant cells self-destruct.

To address these issues and respond to public inquiries that led to the distribution of over 75,000 oral cancer publications last year, NIDR has formed a collaboration with NCI to support as many as four new national centers for oral cancer research. We are also working closely with public and professional organizations, including the American Dental Association, the Oral Health Coalition, organized professional baseball, and a number of community-based health and education programs designed to reduce the risk factors for oral cancer. Our newly funded Regional Research Centers for Minority Oral health are also addressing oral cancer research. Our goal is to provide scientific and health information that can work to eliminate or reduce the behavioral and environmental risk factors while we tackle what can be done at the molecular and genetic level to prevent or reverse the cancerous process. In addition, I write a monthly column for the Journal of the American Dental Association, which is read by 140,000 dentists in the country. In the forthcoming April issue we provide comprehensive information addressing the professional responsibilities related to health promotion, oral cancer examinations, treatment, and suggestions for reducing risk factors. Finally, NIDR is planning to use television to reach large numbers of people, such as planned announcements during baseball games to discourage children and adolescents from using spit tobacco.

The three initiatives I have highlighted, focusing on birth defects, bone and tooth biology, and oral cancer illustrate the extent to which NIDR is poised to address some of the most serious health problems America faces today. Each exemplifies an area where NIDR has made impressive progress over the years and stands ready to partner with other NIH and federal agencies, with the private sector and foundations, to accelerate progress and move us further toward fulfilling the promise of improved diagnostics, therapeutics, and ultimately, the means to prevent disease.

I very much appreciate this opportunity to provide the members with a sense of our current and future directions. Mr. Chairman, the FY 1997 budget request for the National Institute of Dental Research is \$174,463,000. I will be happy to answer any questions.

Harold C. Slavkin, D.D.S.

Dr. Harold C. Slavkin, D.D.S., is the sixth director of the National Institute of Dental Research, which was established in 1948. Dr. Slavkin had previously directed the Center for Craniofacial Molecular Biology at the University of Southern California (USC) School of Dentistry. He assumed the NIDR position in July 1995.

As director of NIDR, Dr. Slavkin oversees a staff of about 400 scientists and administrators and an annual budget of more than \$183 million. NIDR investigators and grantees are recognized as leaders in cell and molecular biology studies of disfiguring birth defects, chronic pain conditions, oral cancer, oral infections and immunity, bone and joint diseases, and in the development and testing of new diagnostic techniques and biomaterials. The Institute directs the NIH Pain Research Clinic, located on the NIH campus.

"Many of us in the biomedical research community sense that investigator-initiated research must be defended and maintained, and that new horizons never before contemplated must be explored, in order to advance American Leadership in fundamental and applied biology," said Dr. Slavkin. "In this regard, I plan to do everything possible to be proactive for the biomedical research community and to continue the process of broadening the scope of craniofacial-oral-dental research. I am delighted and privileged to serve as the sixth director of the NIDR at this unique time of opportunity and challenge."

As head of the USC Center for Craniofacial Molecular Biology, Dr. Slavkin directed a team of scientists investigating the genetics of normal and abnormal craniofacial, oral, and dental development. His own studies focus on the developmental processes underlying a number of congenital and acquired craniofacial and oral defects. In addition, he taught molecular biology at the graduate level and biochemistry and nutrition at the USC School of Dentistry. Dr. Slavkin was responsible for creating the first Ph.D. program in the nation in craniofacial biology, a program he chaired for 10 years.

Dr. Slavkin has long been active in programs to support and strengthen precollege science education in Los Angeles. He helped initiate a program sponsored by the National Science Foundation that gives high school students an opportunity to work on a research project at a university. He served as executive producer and writer for a Public Broadcasting Service (PBS) film called "A Lifetime of Change," shown at the 10th Annual Conference of the International Society of Developmental Biology and the Academy of Motion Pictures, Arts and Sciences in Beverly Hills. He also collaborated with PBS on the production of "Genetic Engineering, Why in the World?" and with other educational film companies in the making of "Development and Differentiation" and "Intracellular Communications."

Dr. Slavkin is the immediate past president of the American Association for Dental Research. he belongs to numerous professional organizations, including the International Society of Developmental Biology, the American Association for the Advancement of Science, the American Dental Association for Dental research, and the American Cleft Palate Association. He serves on the editorial boards of the Internal Journal of Developmental Biology, Difference, Oral Diseases, and Current Opinion in Dentistry.

Dr. Slavkin received his undergraduate degree from the University of Southern California in 1961, and his D.D.S. from USC in 1965. He received an honorary doctorate in science degree from Georgetown University in 1990.

Mr. PORTER. Dr. Grady?

NINR OPENING STATEMENT

Dr. GRADY. Good morning. It is a pleasure to be here for the first time as the Director of the National Institute of Nursing Research.

This year has a special significance for us, because it marks our tenth anniversary at the NIH. Over a decade ago, Congress passed legislation that created our organization as the focal point for Federal nursing research. The support of this committee leading up to our establishment and throughout these ten years has been instrumental to our success in addressing the health care issues of the Nation.

Our research addresses cultural, age, socioeconomic and geographic differences. Our goal is twofold: that of improving health and of reducing costs by addressing such problems as low birth weight infants, Alzheimer's disease, and early discharge of patients from hospitals.

Today I will focus my remarks on our progress and plans for the future. Nursing research links biological and behavioral studies. Progress has been made. Results from laboratory studies indicate that a substance called deferoxamine improves blood flow to ischemic brain cells and limits the impact of injury. Recurrent stroke may be prevented through exercise programs, which have the effect of lowering blood pressure.

We better understand how to promote health in the workplace. A recently completed study provides direction for effectively communicating health information to vocational workers.

As we plan for the future, we are concerned with issues of cognitive impairment, pain, and the clinical impact of genetic knowledge. Cognitive impairment is a national health care problem. It accompanies many disorders, including the dementias, AIDS and stroke. Cognitive problems rob people of their minds and deplete their material resources. Our research is directed at preventing or delaying that deterioration.

NINR supports research to find non-pharmacological ways to manage wandering, falls, and sleep disturbances that accompany cognitive impairment. And ways are being identified to help family caregivers deal with these problems.

Pain is a serious threat to good health and recovery from illness. This common symptom generates massive health care costs and lost productivity. The NINR has taken the lead in a major research initiative on pain involving nine other NIH institutes. The collaborative effort examines pain from many perspectives, from the gene to the molecule, from the cell to the whole person. Our focus will be to understand the physical and behavioral mechanisms of pain, such as the interaction of genetic differences and neuroimmune changes. Pain prevention is an important part of this effort.

While scientific research must continue to seek cures, it must also find ways to ease the symptoms of disease and modify problems arising from treatment. Secondary symptoms, such as those associated with cancer treatment and AIDS, can be as life threatening as the disease itself. The NINR supports basic and clinical studies on the biological and behavioral causes of treatment related

symptoms. We want to know at what point in the treatment process do these problems occur and how can they be modified.

Our nursing research program is ambitious, even in these times of downsizing and streamlining. As we look forward to 1997, important work continues to address the challenges that individuals, patients and health care providers face. The fiscal year 1997 request for the National Institute of Nursing Research is \$51,951,000.

Mr. Chairman, I will be pleased to answer questions you may have.

[The prepared statement and biography of Dr. Patricia Grady follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
Statement of the Director
National Institute of Nursing Research

It is a pleasure to be here today for the first time as Director of the National Institute of Nursing Research (NINR). This occasion has special significance, because this year marks our 10th anniversary. Over a decade ago, Congress passed legislation that created our organization as the focal point for Federal nursing research. The support of this Committee leading up to our establishment and throughout these ten years has been instrumental to our success in addressing the health care issues of the Nation. We are very appreciative and we thank you for that support.

Being a part of the NIH has been important to the growth of nursing research and recognition of its contributions to improve health. Our research has always emphasized a multidisciplinary, collaborative approach to fulfilling our broad mandate. This strategy has been amplified throughout the decade, so that today we can point to numerous cooperative research efforts with almost every institute at the NIH. Nursing research findings, once envisioned to affect nursing practice alone, are now understood to be relevant to the work of all health care practitioners.

Our portfolio links biological and behavioral research to address health problems, encompassing studies from the molecular levels on up to the human being. Let me give you examples of recent preliminary findings.

In the basic research area, there is initial promise of curtailing damage following severe head injury. Head trauma is a serious problem that primarily strikes young men between the ages of 20 and 40, resulting in a loss of productive lives and an increase in intensive care and rehabilitation costs. Typically, there is a population of injured brain cells surrounding those killed by the initial traumatic insult. These cells are endangered as decreased blood flow deprives them of nutrients and allows cellular waste products to accumulate. When waste products accumulate, cells die. Using an animal model, a substance called free deferoxamine, which acts as a scavenger for waste products in the blood, was infused intravenously soon after injury. Preliminary results are showing improved early recovery of blood flow and metabolism, which holds promise of saving brain cell lives and reducing the damaging effects of head trauma.

An example of early findings in the clinical research arena provides hope for prevention of recurrent stroke. Stroke patients usually have low endurance for exercise, although physical activity is thought to be important in the recuperative process. When patients with a moderate weakness on one side use an exercise bike regularly for 30 minutes, they improve their aerobic capacity and sensorimotor function, as measured by such factors as sensation, balance and awareness of body position. The exercise training also significantly improves the systolic blood pressure. Since evidence suggests that the level of elevated blood pressure during exercise is comparable to elevated blood pressure

that can occur during daily activities, a lowered systolic level during exercise could ultimately mean a reduction in the risk of a future stroke.

Behavioral research covers a wide area, including prevention of health problems. A study of the lifestyles of vocational, skilled trade, and administrative and managerial automotive and construction workers sought to identify special factors to consider in the development of health promotion programs in the workplace. Using the Health-Promoting Lifestyle Profile, which includes such elements as stress management, exercise, and nutrition, nurse researchers measured the results according to job category, ethnic identification, age, gender and education. Initial findings show that the higher the worker's level of education, the higher the scores on healthy lifestyle components. Job category was the second most significant factor. Other interesting findings show that women scored higher on such factors as exercise, taking responsibility for their health, and interpersonal support. Neither ethnicity nor marital status was a factor. The results of this study indicate that the vocational factory and construction workers are in greatest need of assistance in increasing their awareness and practice of good health habits. These findings suggest that in designing health promotion programs for the workplace, a test of participants, using the healthy lifestyles scale, would help tailor activities to better meet employee needs.

These examples I have been discussing give you a flavor of the broad scope of nursing research. Our program is ambitious, even in these times of downsizing and streamlining. We have already made some changes that show increased efficiency and potential cost savings. For example, we have achieved a more flattened organization with fewer supervisors, and we have combined certain internal structures that promote an increased teamwork approach. We are also sharing management resources, such as the personnel function and office space, with other NIH organizations. Streamlining is an ongoing process, and we will continue to look for opportunities to improve efficiency of operations.

Now I would like to turn to the future and identify some important health issues and our research plans to address them over the next year and beyond. One such issue is cognitive impairment, a significant public health problem that robs people of their minds, reduces quality of life, and raises health care costs. This disease symptom can surface at any age. It appears in many disorders, such as Alzheimer's disease, AIDS, brain trauma, and stroke. To develop interventions to manage or ease cognitive impairment, NINR-supported research will expand the knowledge base concerning the relationship between altered brain structure and function and the type and degree of cognitive responses to the abnormal changes. Interventions that prevent or delay the onset of cognitive impairment will continue to be investigated. Nonpharmacological approaches to manage problems such as wandering, falls, sleep disturbances, and inadequate nutrition, are under development. And assistance for family caregivers is a focus -- to help them interact with cognitively-impaired relatives and to ease caregiver burdens, which can compromise their mood, immune function and productivity.

Another important issue is pain, which endangers both good health and recovery from disease. This common symptom's effects are pervasive in our society and generate

over \$100 billion annually in health care costs and lost productivity. The NINR has taken the lead in a major research initiative on pain that involves nine other NIH institutes. The overall goal is to examine the pain phenomenon at all levels, from the genetic and molecular, to the cell and organ, to the whole person. The NINR focus will be to understand the physical and behavioral mechanisms that compromise recovery and quality of life. Specifically, we will explore mechanisms of controlling pain, looking at such variables as genetic differences and neuroendocrine and neuroimmune changes. Prevention will be emphasized, so that the neural pathways for pain that perpetuate hurtful sensations after the stimulus is no longer present do not become permanently established.

The speed and importance of genetic discoveries is the driving force behind the urgent need for knowledge about clinical ramifications, the effects on people's lives, and the help health care providers can give. Nursing research is contributing to these and other concerns, including genetic screening, lifestyle modifications to prevent or delay genetic expression of disease, and the implications of gene therapy. NINR-supported studies will focus on the difficult decision-making process that individuals and their health care providers must face, such as who should be tested and when, and whether social, ethical and financial consequences can be borne satisfactorily. Multidisciplinary research will also be supported to address how to prevent or alter the progression of disease in persons with genetic predispositions, including helping people make vital lifestyle changes, such as taking extra precautions that would avoid known disease-inducing agents.

We must find new and better medical treatments for illness, but it is also critical that we find methods to ease the deleterious symptoms that may frequently accompany existing treatments. Sometimes secondary symptoms can be as discomforting and life-threatening as the disease itself. Examples include nausea and vomiting, depression, and fatigue, which are often associated with treatments for such illnesses as cancer and AIDS. The NINR will support basic and clinical studies on the biological and behavioral causes of treatment-related symptoms -- when these problems occur in the treatment process, and how they can be ameliorated.

Another issue associated with treatment concerns individuals who do not adhere to treatment regimens, often to avoid unpleasant side effects. Serious consequences exist for their own health and, we now know, the health of others. The emergence of infectious diseases resistant to drugs, such as the new virulent form of tuberculosis, is partially attributable to poor compliance with treatments. Studies will investigate the influence of physical, cultural, socioeconomic, educational, and psychological factors on treatment adherence.

Chronic wounds, such as pressure sores, present a major health care problem. Pressure sores alone afflict up to 15 percent of all hospitalized patients and up to 35 percent of nursing home patients. If untreated, they can lead to serious systemic infection. These skin wounds are caused or influenced by many factors, such as immobility associated with a decreased blood supply, friction of the skin against bed linens, and thinning of the skin often seen in the elderly. NINR research will include

managing chronic wounds and preventing pressure sores in those with spinal cord injury. In collaboration with several institutes of the NIH and other agency members of the Skin Interagency Committee, we will also examine the cellular and biochemical processes associated with chronic wounds to develop information pertinent to prevention or treatment.

A frequently mentioned component of health promotion and prevention of disease is physical activity, including regular exercise. Important for all age groups, sufficient physical activity can, for older adults, mean the difference between independent, injury-free living and confinement to an institution. Today, many older Americans are not physically fit. Up to 40 percent of Americans older than 75 cannot climb 10 stairs, lift 10 pounds or walk a quarter of a mile. Seventy percent of older Americans do not exercise regularly. An objective of NINR is to investigate the effectiveness of increased, regular physical activity in improving the health of older adults. We will also examine the relationship of physical activity to such factors as gender, social interactions, and environmental conditions. The impact of regular exercise regimens and the amount required to improve strength, metabolism, balance, endurance and aerobic capacity will also be investigated.

These are our major research priorities for fiscal year 1997. Important work continues in other areas to address challenges that individuals, patients and health care providers frequently face -- urinary incontinence, the unhealthy behaviors of young people, low birthweight infants, hip fractures, AIDS, menopause. Our research is responsive to cultural, age, socioeconomic and geographic differences. We seek the twin goals of health care effectiveness and cost effectiveness. And most of all, we seek to assure that the scientific agenda has a human aspect -- one that is directly relevant to applying research findings to improve the Nation's health.

The FY 1997 request for the National Institute of Nursing Research is \$51,951,000. I will be pleased to answer any questions you may have.

PATRICIA A. GRADY, Ph.D., RN
Director
National Institute of Nursing Research
National Institute of Health
Bethesda, Maryland

Dr. Patricia A. Grady is the Director of the National Institute of Nursing Research (NINR) at the National Institutes of Health (NIH) in Bethesda, Maryland. Appointed in April 1995, Dr. Grady leads the Institute in its support of research on the biological and behavioral aspects of critical health problems that confront the Nation.

Before coming to the NINR, Dr. Grady was Deputy Director of the National Institute of Neurological Disorders and Stroke (NINDS) at the NIH. Prior to this, Dr. Grady was Assistant Director, then Acting Director of the NINDS. She came to the NIH in 1988 as a program administrator for NINDS's extramural research programs related to stroke and brain imaging. While there, she served on NIH's Task Force for Medical Rehabilitation Research.

Dr. Grady's scientific research has been primarily in stroke, including arterial stenosis, cerebrovascular permeability, cerebral edema and hypertension.

A member of many scientific organizations, including the Society for Neuroscience and the American Academy of Neurology, Dr. Grady is a fellow of the American Heart Association Stroke Council and was recently elected a member of the American Neurological Association. Internationally known in the field of stroke research, she reviews major journals and speaks on neurological sciences, nursing research and federal research opportunities.

Several special committees she serves on include the Society for Neuroscience's Ad Hoc Committee on the Decade of the Brain and the Steering Committee for The Decade of the Brain of the American Academy of Neurology.

Dr. Grady is also a member of Sigma Theta Tau, the nursing national honor society and the American Nurses Association. In addition, she has been active in the Council of Nurse Researchers.

In August 1995, Dr. Grady received the Public Health Service Superior Service Award for her exceptional leadership as Acting Director of the NINDS. She is also a recipient of the NIH Merit Award. Dr. Grady was selected the 1995 Excellence in Nursing Lecturer by the Council on Cardiovascular Nurses of the American Heart Association.

Before coming to NIH, she served on the faculty of the University of Maryland School of Medicine. During that time, she was also a member of the faculty of the University's School of Nursing.

Dr. Grady has delivered numerous invited presentations over the last six years. These span scientific issues in the area of stroke and brain imaging, the neurological sciences and neurological disorders, rehabilitation, and opportunities in the neurosciences, as well as grant writing and the grants process.

Dr. Grady earned her bachelor of science degree in nursing from Georgetown University in Washington, D.C. She received her masters degree in nursing and her doctorate in physiology from the University of Maryland School of Medicine. Her thesis work was in cerebrovascular physiology and alterations in intracranial pressure.

RISK ASSESSMENT

Mr. PORTER. Thank you, Dr. Grady. And let me thank all of our panelists this morning.

I'm going to start with questions for the entire panel. This is, as you know, an experiment that we are conducting both Monday and today. And I hope the questions will be relevant enough to the work of all of you, or at least some of you, that you will be willing to answer. I'm not going to direct the question to any of you in particular, I'm just going to ask you if you wish to respond to it, to do so. And as many of you who wish to respond can do so.

First, several of you talked about risk factors and the fact that we may discover through mapping of the human genome system genes that tell us an individual is at risk for some particular disease. I think, Dr. Slavkin, you talked about oral cancer and looking at the genetic base for that. And I believe you also said that tobacco and alcohol are particularly involved, if someone has that predisposition.

My question for all of you is, we're spending, of course, a lot of time attempting to find genes that provide the basis for disease. But once we find them, we also have to be concerned with the behavior that we seem to be able to determine is a negative factor. And yet often, even when we determine that certain behavior is negative, people engage in it anyway. And we can go from tobacco to overeating to a number of different things that affect disease.

So is it really going to be that much of a payoff in terms of preventing diseases by finding the genetic base, or are we simply going to be telling people something that really won't change their behavior much at all? What do you think?

Dr. SLAVKIN. It's a very, very superb question. All of us sitting here are obviously in partnership with a much larger community. After a gene is cloned in sequence, and after we know that a particular gene is involved in the mechanism of converting a normal cell to a neoplastic cell, once those risk factors are identified, then we need to partner, and I think many of us are attempting to do that, with a number of other change agents, such as K-12 education and the sports coaches who look after baseball vis-a-vis spit tobacco, which is fashionable for many youngsters.

By working with models who have a very significant impact in communities, the coaches of the sports teams, the teachers in the schools, by writing articles and going out and mixing with the men and women who are literally at the front line in dental offices and medical offices around the country—roughly half of the population see their dentist every year—we can effect changes in behavior.

I wrote a column, which is in the April issue of the Journal of the American Dental Association, to try to further stimulate my colleagues in dentistry, that they have a tremendous opportunity and I would think a requirement to try to be more proactive in translating scientific information into modifying the behavior of their patients.

Dr. GRADY. If I may add something, Mr. Chairman. We fund a number of studies of risk assessments, trying to get people to engage in behaviors that are healthy lifestyles. Several particular projects come to mind. We are collaborating in the area of cancer

with the National Cancer Institute and also the National Institute on Aging in trying to get older women who are at a much higher risk for not only the development of cancer but for a higher mortality rate from breast cancer, to get those women to come in for screening.

One approach is to get younger women who are more in tune with the information that's available to talk about breast cancer screening with the older women in their families or in other settings. In addition, since health care is moving so quickly out of the hospital and into other settings where nurses predominate, we have opportunities to address people in their homes as well as in clinical settings.

Another investigator in the Midwest is studying smoking cessation in an effort to address the people who are at high risk for lung cancer. This investigator has studied a number of ways to alter behavior rather successfully, and is now looking at protein markers and immune system responses. We have other such examples, but I will let someone else address this issue.

Dr. HODES. I would also be happy to respond to your question by making two points. The first consists of what you've heard already, relating to those risk factors for which there are apparent behavioral responses or interventions. I mentioned the identification of risk factors for falls in older people, and the fact that this information had been translated successfully in experimental studies into a substantial 44 percent reduction in falls. This is not the end point of success. What's clear from these studies is that translation of these findings into broad-based behavior modifications across the country requires basic research into the motivation of behavior so that we can understand differences between men and women, between old and young, and across ethnic groups, and devise the strategies that are going to be most effective in each of these groups.

At another dimension, you talked about the identification specifically of genetic risk factors. And I think what we're all appreciating here is that the identification of these genes, which are enormous scientific breakthroughs themselves, is only a beginning that will usher in a new dimension of biomedical research, in which we understand how those genes work, and whether the means by which they work provide the basis for biological as well as behavioral interventions and interactions.

So I think we're cognizant of the fact that we want not to underestimate the importance of the genetic breakthroughs, and yet not to leave the public with a false expectation that the genetic identification is itself the end point and victory. It's a very critical victory, but only one step towards ultimate translation of this information into intervention to cure or to prevent disease.

Dr. KATZ. I think you've already heard from other institute directors about the double-edged sword with regard to genetics information in terms of people altering their behavior as a response to knowing what genetic information they carry. And it's very important that we very carefully bring this to the fore, so that the population is not thrust with information that they can't deal with or that we can't deal with yet. So there has to be a move, along with

the genetic information, about how to handle that genetic information from an ethical standpoint, educational standpoint, etc.

I would also like to underline the point that Dr. Hodes made in terms of identifying genes that make people susceptible to disease. Within the NIAMS institute, we have supported innumerable studies that have demonstrated, for example, in certain skin diseases, there is a specific gene that results in a particular disease.

Well, that has enabled us to understand how that skin is put together and how we can intervene to repair that particular area. Perhaps the greatest challenge of all is that most of these diseases are probably multi-genic, so that when one does large scale gene studies, once you find the genes that make you susceptible to disease, studying the pathophysiology and cell biology is really the next great challenge.

RISK FACTORS

Mr. PORTER. Let me ask another question along this same line. As we map the entire genome system of human beings, will we some day then be able to do a profile on an individual, they will go to their physician and the physician will have the means somehow to do a complete profile of their genetic makeup and determine what risk factors they may particularly have, and be able to describe those risk factors to that individual, and also tell them what behavioral changes may help to avoid the diseases that might be possibilities for that individual? Is that where we're headed in all this? I just want to look ahead. If so, when is this going to happen?

Dr. KATZ. The "when" question I think I won't address. But for the question of susceptibility to certain types of diseases, let me use one example, susceptibility to melanoma. There is a genetic predisposition to melanoma. If one knows that he or she carries such a gene or such a complex of genes, the physician will know, will be able to reinforce to that patient that one has to be far more cautious in terms of exposing oneself to risk factors. And that's where I think it becomes a very important thing. But translating knowledge into behavioral change is a tremendous challenge.

Dr. HODES. I would continue along that theme. I think that the first part of your question, whether at some point in the not too distant future, it will be possible for a physician in principle to communicate information about the entire genome of a patient, which will carry with it information about multiple risk factors, is probably not so far away.

The translation of that, however, will vary enormously over a spectrum of risk factors. Dr. Katz has talked about the kind of risk factor that I think we are most happy to identify, that which carries with it an apparent implication for behavior and intervention that can really make a difference.

There are other varieties of risk factors which have different implications. Those, for example, for which the majority, unfortunately, to date we don't have definitive interventions. The implications of communicating to an individual the fact that he or she carries a risk factor and the impact that has on life at a time when we may or may not know how to intervene, coupled with what you clearly have been addressing at great consideration, the legal, in-

surance, and ethical considerations are aspects to which we give a great deal of attention.

And our objective, I think, is to have matured the science of ethics communication and these considerations in parallel with the maturity of the scientific field, so that we are to the degree humanly possible, able to combine human considerations of this sort with the dissemination of genetic information which is going to become progressively more available in years to come.

Dr. VARMUS. This is an issue which obviously addresses the entire NIH portfolio. I might say a word or two about it.

In a sense, we're already doing what you're asking for, that is, when the patient goes to a physician for a complete evaluation and gets a blood cholesterol, has blood pressure measured and a number of other things, in a sense, that constitutes an evaluation of what we call the phenotype, which results from multiple genetic factors as well as environmental factors.

In my judgment, we will never be sequencing the entire genome of every patient. At some point in the future—and it probably is not so far off—there will be a genetic analysis done that will allow people to be screened for certain fairly common genetic markers. None of us wants to see that happen before we have in place the legislation that will protect them against discrimination from insurers and employers.

SHARED RESEARCH AREAS

Mr. PORTER. Thank you, Dr. Varmus.

There are some obvious areas of research that all of you share in common, such as the development and preservation of bone and tissue and certain behavioral science issues. But what other research areas less obvious to the layman do you share?

Dr. HODES. I think, as Dr. Varmus alluded to in his introductions, we can identify examples of research common to twos, threes and fours among this panel, as well as others which also involve many institutes not represented here. One area of prime interest to the Aging Institute is Alzheimer's disease, an area in which the Nursing Institute, together principally with the Neurology and Mental Health Institutes, have strong investments.

And our commitment in this area, which I think is typical of other examples you hear as well, is to take advantage of the diversity and perspectives that different institutes bring. In a case such as this, the Aging Institute obviously has a strong perspective on aging, normal aging and changes in the central nervous system; the Nursing Institute, in terms particularly of care and caregiver issues, has its own emphasis, as do the Neurology and Mental Health Institutes.

In addition to perceiving these strengths, I think in each of these cases we share an understanding of the need to coordinate efforts, so that rather than being wasteful or redundant, we actually capitalize and synergize by virtue of our cooperation. In the case of Alzheimer's disease, there is constituted an inter-institute work group, which meets on a regular basis. The import attributed to it by the institutes involved is reflected in the fact that to date, in each of the meetings, all four institute directors have chosen to be present, to allow coordination of our efforts.

Dr. KATZ. I would underscore that. I think that in addition to the four of us, for example, in the area of osteoporosis, there are many other institutes and centers that have a keen interest in bringing to the table some of their expertise. And this is coordinated through the group that I mentioned, the Federal Working Group on Bone Disease that encompasses not only NIH, but other Federal agencies.

In addition, from the standpoint of the Arthritis, Musculoskeletal and Skin Diseases Institute, we have tremendous interactions with the Allergy Institute. As you heard, a lot of the diseases that we are studying are autoimmune diseases. So they have immunological elements, some of which are studied by the Allergy Institute or supported by the Allergy Institute, and others which are supported by our institute.

As well, a final example, and there are many others one could give, is in the area of skin cancer. We're particularly interested in the biological effects of ultraviolet radiation. We support considerable studies in this area. We support studies in how the skin is affected by ultraviolet radiation. The Cancer Institute as well is studying what some of the genes involved are in terms of the development of not only non-melanoma skin cancer, but also melanoma skin cancer.

So there's tremendous crossover in our institutes in terms of our interest. But we bring something special to the table in each one of these instances.

Dr. GRADY. I think another area that is not as obvious to the general public is that of chronic wounds, in which we collaborate with several institutes, but in particular NIAMS and NIA. The issue of chronic wounds, such as pressure ulcers, stasis ulcers, diabetic ulcers, is a major problem in terms of disability across the Nation in people who are in hospitals for short periods of time and in people who are out in their own community and in nursing homes.

Together we are looking at a variety of issues related to wound fluids and composition of those fluids in order to determine who is at risk. We have developed scales to determine who would be at risk for chronic wounds and how to intervene as well.

We are also collaborating with the Allergy Institute in HIV, given that patients are living longer now with AIDS and HIV, these issues of quality of life and also symptom management become very important.

Dr. SLAVKIN. I wanted to capture the less apparent relationships. And one which I don't know if it's been mentioned as yet is the experiment that Harold Varmus is running at the NIH in recruiting many of us to come to the NIH and be part of another institute in terms of intramural science. I think this experiment should be watched closely, because it is another way of engendering a less than obvious relationship between a number of us.

Another area that is not intuitive is using saliva as a body fluid to diagnose a whole host of disorders from drug abuse to estrogen deficiencies to all kinds of endocrine problems to a number of diseases found throughout the body, so that the oral cavity, vis-a-vis saliva, is a very informative way of making a diagnosis. A number of institutes are sharing that kind of insight.

INSTITUTE COORDINATION

Mr. PORTER. I was about to ask Dr. Varmus the extent to which his office gets involved to ensure that coordination occurs and whether that has any relationship to using your 1 percent transfer authority. Can you respond to that?

Dr. VARMUS. Yes. We are looking closely at coordination among the institutes. Sometimes this is something that the Office of the Director is mandated to do, because we have coordinating offices in the OD, or we have been asked to help develop coordinating offices for sleep disorders, for example, or for nutrition that are housed in the institutes.

But I also take an interest in what's happening with diseases like Alzheimer's Disease or osteoarthritis or osteoporosis that we know involve many institutes. And I do watch that fairly carefully.

I have in some cases used my 1 percent transfer authority to help to create synergies among institutes with coordinated activities. Two such examples are illustrated by our request for 1 percent transfer, which is about to come to your committee, one in the area of neuroscience—which we discussed on Monday—and the other in the area of bone diseases, involving two of the institutes represented at this table—NIAMS and NIDR.

COORDINATION OF RESEARCH EFFORTS

Mr. PORTER. Let me ask these next two questions together and you can respond to whatever portion you'd like.

Does each of you know what the other institutes are spending in areas of research you share? Are you familiar with the composition of their grant portfolios in these areas? If one of you is unable to fund a particular grant in a common research area, do you offer it up to the other institutes for possible funding?

Dr. HODES. I think these are important questions as they reflect how well we really are coordinating efforts. In the case of Alzheimer's research and the work group which I mentioned, our format is intended to address very explicitly the concerns you raise. That format is to specifically compare grant applications and portfolios in areas of Alzheimer's research, and to explicitly do so in a timely fashion that coordinates with the funding cycle. If there were grants that cannot be funded in a given year by one institute, they can be considered for funding by another.

Our attempt is to make as seamless as possible the familiarity and awareness across institutes of the portfolios of research being supported.

Dr. KATZ. I would reiterate that—and add to it—that there is a commitment of the institute directors that is sensed at the program level that we are in this together and that we are trying to facilitate the best possible research that's out there.

So for example, Dr. Hodes and I have begun meetings not only between our program staff, but with ourselves, physically there, to talk about these issues. Other institutes are coming into these discussions, so that we can identify particular areas of mutual interest. We do know what the other institutes are doing. Fortunately, we are, in the NIAMS institute, blessed with outstanding program

directors who keep us very well informed with what their colleagues are doing at other institutes.

PREVENTING DUPLICATION OF EFFORT

Mr. PORTER. And now the opposite side of this coin. Are there any safeguards in the peer review system to prevent duplication of effort? For example, what if four researchers submitted nearly identical grants with very good scores, but they happen to be assigned to four different institutes by the Division of Research Grants? Could each receive funding? This may be a question for Dr. Varmus.

Dr. VARMUS. It could happen. One would hope that the referral process would not assign those to four different institutes. Even if they're assigned to the same study section, they may all end up getting very good scores, because there they would be evaluated for scientific merit. Then it's up to program staff to decide how to handle such a collection of grants.

That may be a very difficult situation. Because frankly, if the grants address an area of high priority and they're all equally excellent, it may be difficult to choose among them or avoid funding them all. In general, scientists don't want to do exactly the same experiment that someone else is doing.

The review process is a confidential one, but the individuals who are working in any single field are meeting at scientific conferences and talking to each other. One would hope—and in general I think it's true—that scientists try to find individual paths that allow them to do work that is individually creative.

You're touching on an issue that at times we can't avoid, especially when an area is especially exciting intellectually and very productive people do head for it. And sometimes we see results that go beyond the simply confirmatory to the multiply confirmatory.

Dr. KATZ. I think there's an added dimension to that, and that is, what happens if all four are on identical subjects in the same institute. That is again a complex issue. And fortunately there again, our program people deal with that. That is an issue for each of us in terms of priorities.

Dr. SLAVKIN. And sort of spinning it about 180 degrees, every once in a while, a group of investigators who are interested in the same problem apply as a cluster on purpose, where each of them is taking a particular slightly different but complementary part. The NIH provides a mechanism for this collaboration.

So they create almost a thematic program like a thrust of research, but through investigator initiated RO1 mechanisms. That can be very, very effective, since the sophistication of modern cellular molecular developmental biology is such that it's rare to have all the ingredients within one laboratory. So sharing purposefully is another venue that is currently being pursued.

Dr. GRADY. The problem also exists in our community, but it's not quite as critical, because it's a smaller community, and we have fewer study sections that address the research that we fund. The investigators tend to talk to each other quite a bit about what they're doing. But our program people are vociferous in seeking out opportunities, and also in keeping on top of what's going on. We have the advantage of being a newer field.

SCIENTIFIC EXCHANGE

Mr. PORTER. As part of the next question, perhaps you could tell us in which institutes your directors have your personal labs. And the question is, is there much exchange among institutes in staffing? Do scientists and administrators tend to spend their professional lives in one institute or do they rotate among institutes with similar research missions?

Dr. HODES. My own laboratory is in the National Cancer Institute. In terms of the second portion of your question, I have seen in the senior staff, both scientific and administrative of our own institute, a good deal of movement across institutes, often with a very healthy degree of cross-fertilization and sharing of ideas and concepts.

Dr. KATZ. My laboratory has been, for the last 22 years, in the Cancer Institute. And the branch that I am chief of is the Dermatology Branch, which is also in the Cancer Institute. I would agree with Dr. Hodes that there is some movement, but not a lot of movement, of personnel between institutes. For example, the scientific director of the Aging Institute has had a lab in the Cancer Institute for the last 15, 16 years. So there is movement in that way. And that certainly enhances the interaction and knowledge base, not only within the intramural program, but also within the extramural program.

Dr. SLAVKIN. My situation is a very new one. I've been at the NIH for about 10 months. My laboratory is within the Arthritis Institute. Dr. Katz is my boss in that context, a delightful boss, by the way.

I'm noticing that one of the real fluent moments within the intramural program are the post-docs who don't seem to know the boundaries of one institute or another, so that I've recruited people to come into my lab, which is a wonderful benefit for me. I am finding myself meeting lots of people in the Child Health, Diabetes, Neurosciences Institutes, because the scientific expertise is found all over the intramural campus. We can benefit from that, and I think do in a very significant way.

Dr. GRADY. I'm the outlier in that I was a program administrator in the extramural program. And there was a conflict of interest there. Now that I am in the Nursing Institute as the Director, I'm most welcome in the Stroke Branch of the Neurology Institute, where I used to be. Previously it would make them uncomfortable because I had a potential conflict of interest as the Neurology Acting Director. But now, I attend their seminars and help in development of ideas. I also chair sessions in the extramural scientific meetings and serve on editorial boards in the area of stroke.

Dr. KATZ. If I might just add, I think Dr. Varmus brought this up in his opening statement, but a real positive within the intramural program has been the establishment of the inter-institute interest groups. That had been going on for a very long time within the immunological community, and that's how we have interacted, actually, all of our professional lives.

But now there are about 50 inter-institute interest groups, where there is really a symbiosis of activity on the campus. So the walls really don't exist on the campus very much.

PAIN RESEARCH

Mr. PORTER. Pain research seems to be an area relevant to all four institutes. Can you describe recent findings related to pain in your research portfolios? Do these findings suggest new strategies for managing the chronic pain conditions affecting the aging population?

Dr. SLAVKIN. I would love to respond from the National Institute of Dental Research's perspective, to suggest two areas. It's been learned that there is a receptor when excited that is associated with chronic pain. The receptor is called NMDA. And this receptor is the target for trying to suppress it with analgesics.

That work has gone from cloning, a genetic molecular approach, to slices of the brain to screen various candidate analgesics, to animal models to produce chronic pain and then test various analgesics, to the use of modern non-invasive brain imaging techniques, to discover new neural pathways and to learn how that information is processed by the central nervous system.

That is one of the areas at the NIH where work at the bench goes into the clinical center. There is a logic to it that would be very difficult to achieve in many university settings, but fairly easy to achieve within the NIH community. We're very proud of that part of the pain effort at the NIDR. And that of course is also with other institutes that we collaborate with.

Dr. GRADY. One of the studies that we're funding in the area of pain in the elderly is in the early stages of collaboration with NIAMS. This is a program dealing with the elderly with arthritis and includes an exercise program in order to increase activity. Unfortunately, there is a tendency for that population to decrease activity because of the discomfort. Through a prophylactic exercise program, we have been able to show that this population can in fact engage in more activity, to prevent some of the disability related to inactivity.

Dr. KATZ. The crippling that I spoke about with regard to the diseases of the NIAMS is in large part due to the pain component of many of the diseases of arthritis and musculoskeletal disease, and even with regard to skin wounds. We not only support fundamental mechanisms, but in each of these areas, investigators are studying what it is that produces that pain, or what central nervous system abnormality could underlie, these symptoms.

So for example, in fibromyalgia, a common disease, but a disease we know not so much about, there has been tremendous emphasis on what it is that produces the pain, the tender points in patients with fibromyalgia. Recent studies using a new imaging technique have demonstrated a decreased blood flow going to the brain of patients with fibromyalgia. This finding may underlie a decreased threshold for pain in these patients.

These types of studies may be useful in other areas. As well, low back pain is another area where there are probably a multitude of causes for the pain. Studies that we have recently begun to support are addressing the acute low back pain, and what the predictors are for chronicity in back pain. In mid-July, we're having a conference that deals primarily with pain, that is, the neuroscience of pain. We're using fibromyalgia as the paradigm, but I'm sure that

this will lead to important information in other areas. For example in arthritis, osteoarthritis, and rheumatoid arthritis, pain is also a major problem. So in identifying or in trying to identify those gaps in knowledge, we hope that studies in one area will have an impact in other areas as well.

Dr. HODES. You've heard already about the areas that overlap with the interest and mission of the Aging Institute with regard to pain. In addition, the areas of specific concern are at the biological and neurologic level, and the changes in the way perception of pain and other input stimuli alter with age. There is a good deal of evidence that a lot of brain function, even to apparently the same task, is mediated by different areas of the brain, at different ages.

At the behavioral and patient care level, there is a great deal of concern in the way symptoms are perceived by older individuals, and how medical providers respond to the pain and other symptoms of older people as compared to younger. Responses are not always the same, sometimes appropriately, but with questions to be asked about whether the relationship between patient's perception of symptoms and their relationship to caregivers is optimal for relief of symptomatic pain in older people, as well as in younger.

EXTRAMURAL COLLABORATION

Mr. PORTER. As you were all describing the degree of collaboration, interaction, and in sharing that you have within NIH, and on the Bethesda campus, I was wondering if you could contrast what happens in the extramural community along those same lines. Is this something unique to the structure of NIH, or do you find this in major research universities as well?

Dr. HODES. It's certainly my perception that there's little or no contrast to be made. I take that as a tribute to the intramural NIH system and its similarity, in this case, to academia. The identity of administrative entities, departments or institutes is critically important to assure that emphasis is placed in areas of importance. But once those walls are established, it's critical that science and scientific creativity are free to cross those boundaries. Dr. Katz mentioned the example of immunology, and I think equally true in many sciences, on the NIH campus or elsewhere, one would often find it difficult to identify precisely which institute a given investigator is working in as he interacts with his colleagues. I would stress that there is a real dualism. Each institute exists because it carries out a specific mission and recruits scientists to carry out that mission. But all of those missions collectively are best accomplished when the creativity of science is not bound by the walls between them.

Dr. GRADY. I would just like to say that I agree with what Dr. Hodes has said. But I do think that because of the nature of the kinds of scientific questions that are being asked that that is changing on the university campuses as well. Nurse researchers are newer players on most of those campuses and have the advantage of starting out when the climate is becoming more collaborative.

We all know the days of the scientist in their little closet doing an experiment are over. And the nature of the questions now require a collaborative effort in many more cases than they used to.

So I do think we are seeing a change in climate, at least from the nursing medical interaction point of view.

Dr. KATZ. And I think we are proactive in this regard. Because these same program staff and institute directors play a role in not dictating but strongly encouraging interaction. For example, in some musculoskeletal diseases, the interaction between the rheumatological community and the orthopedic community is absolutely critical. Together they contribute more than each community does on its own. In the areas of skin immunology and of immunology underlying many of the arthritic diseases, we encourage this type of interaction in some of the programs that we fund.

Dr. VARMUS. I might comment briefly, having come recently from the extramural community myself. At the universities, the boundaries are not set so much by the institutes at NIH that fund the research as they are by the departmental structure, particularly at medical schools. In basic science departments, in particular, those boundaries have been overcome recently at many campuses, including the one I used to belong to, the University of California at San Francisco, by constructing graduate programs that reach across departments.

That's a pattern which is now in evidence in many places. I agree with Dr. Katz that to the extent to which NIH can continue to fertilize across departmental boundaries by generating meetings and by showing evidence of intersection of disciplines at the science management level, we are fostering healthier connections between disciplines.

COMMON GENETIC LINKS

Mr. PORTER. Throughout the hearings, we have learned of the increasing importance of genetic research in nearly all NIH disciplines. Are there common genetic links to some of the varied disorders the four of you study? Are there genetic research techniques that have been developed in one of your research areas that can be translated to the others?

Dr. HODES. A brief global answer to the latter part of your question is that the techniques that have been developed for identifying and mapping genes and studying their expression are universally developed and applied in the areas of research supported by our four institutes, as well as the rest of the institutes across NIH. These are techniques and tools that serve the tasks and missions of multiple institutes.

Dr. SLAVKIN. From another point of view, and one that is extremely exciting as a practitioner of science, a gene, for example, called *MSX1* was analyzed up by a cardiologist in Boston because it was expressed during heart development. It then turned out that it was responsible for tooth development. It then turned out that *MSX1* was relevant in bone and suture formation between the interfaces of different craniofacial bones.

It's a little bit of a puzzle that begins to unwind and become a little bit clearer, by using the same methods, modern molecular biology, and the same lines of evidence. Null mutations in transgenic animals, for example, is a methodology that is shared by almost all of us, irrespective of which molecule, whether it's a receptor or whether it's a growth factor or whether it's a transcriptional factor.

And that commonality means that we speak the same language, we understand the approaches, and we benefit from one another.

Dr. HODES. I would like to elaborate on the example of Werner's Syndrome, which I'd mentioned earlier, that was uncovered by investigators studying it as what has been dubbed the premature aging syndrome. Patients with Werner's Syndrome, due to a mutation of a single gene, have changes in skin and hair, acceleration of cardiovascular disease, of diabetes, of cancer, and of osteoporosis—although it is a different distribution of osteoporosis than seen in normal cases. This is an example of a single lesion in a helicase affecting DNA metabolism and replication, that is going to be of interest for multiple disease and organ oriented investigators.

Dr. GRADY. We have a very large interest in this area as well, in that for the genes that are being identified, the small number that will lead to a one gene—one disease sequence is offset by the majority which will predispose to an illness, as you mentioned earlier. This issue was previously addressed. What that does is impact very largely on the nursing community who will then be part of the risk assessment in addressing alterations of behavior.

With the Genome Center, we're collaborating intramurally on shared post-docs on nursing and genetics, and also working with the Genome Center to address the issue of nursing and education. As Dr. Collins mentioned earlier this week, the number of genetic counselors available is far less than what we anticipate needing. We are working together to develop ways that nurses can help to address those issues, both the testing issues and the ethical issues.

Dr. KATZ. I know you don't need convincing, but science is really exciting. For example, the development of animal models of disease has provided considerable information in terms of the mechanisms involved in some of the diseases that we're interested in.

Our illustrious leader, Dr. Varmus, is a world-renowned expert in the *src* gene, and now he's working on bone diseases. Why? Because he and his colleagues prepared a type of mouse where this *src* gene was knocked out, that is deleted, and what they found is that these mice developed a bone disease called osteopetrosis. And now, looking at this whole family of genes, it's becoming extraordinarily interesting to try to manipulate bone and bone formation. These findings thus provide us with a whole new dimension of study.

The same can be true with models that have been developed for immunological disease. Basically if one knocks out or gets rid of a gene that encodes for a certain type of cytokine or protein, one ends up with certain types of bone diseases. This information enables us to take the field that much further along and ask similar questions in human beings.

Mr. PORTER. My first conclusion is that we need more microphones. That's one conclusion.

Dr. KATZ. You are a scientist. [Laughter.]

Mr. PORTER. My second conclusion is that I wish this were a day when the House was in session and more of our members could be here. Because I think it is infectious, actually, to watch the interaction between the five of you in this case. And the excitement that you bring, as you said, science is exciting, to not only your own

work but the entire work of NIH and the scientific community. And I wish our members could see that and understand it a little bit better. But we went out of session last night and don't have them here.

At the end of all of this, I think what we will do is ask the Monday panel and this panel to give us their comments on this, although three of you have not testified individually before. Dr. Grady, you testified individually in neurology. And Dr. Slavkin was here last year, and watched the individual testimony. Dr. Hodes has testified and Dr. Katz, I don't—

Dr. KATZ. New kid on the block.

Mr. PORTER. Were you here last year?

Dr. KATZ. I was not.

OSTEOPOROSIS

Mr. PORTER. I didn't think so. But perhaps you'd like to comment upon this format, and I'm going to finish with individual questions for each of you. But others might want to comment upon the same area. Let's see what happens with that.

Dr. Katz, your testimony briefly mentions the role of fluoride in preventing fractures relating to osteoporosis. Can you tell us more about these findings and whether it is premature to recommend fluoride supplements, a fairly simple treatment, for those prone to fractures?

Dr. KATZ. This has been an area of considerable study for many years. And it was initially thought that fluoride would be useful to increase the integrity or enhance the integrity of bone. However, although fluorides will enhance bone growth, they will enhance bone growth that is not really too well organized. And that was the problem with the utilization of fluoride for therapy, for example, of osteoporosis.

The recent studies that have been reported in this past six months on the effect of slow release fluoride makes the claim that there are decreased fractures in the spine, with ingestion of this slow-release fluoride. That has been questioned by many people. And the question still remains as to what is the integrity of the bone that's being made. It's not that we're just looking to lay down bone. But we're looking to lay down good bone, as opposed to bone which may even be more prone to fractures.

ALZHEIMER'S DISEASE CENTERS

Mr. PORTER. Dr. Hodes, we are approached from time to time by groups who want us to direct you to expand the Alzheimer's disease research center network. I believe you now have more than 55 of these centers and satellites. Within the pool of resources allocated to your Institute, would you favor increasing the number of Alzheimer's centers?

Dr. HODES. There are currently 27 Alzheimer's Centers with 26 associated satellite clinics. It is an extensive network, supported with a budget of approximately \$37 million a year, that carries out a number of important coordinated efforts in basic research and in clinical studies. It's highly effective as a consortium. I think it has reached a very substantial size, which serves its mission well.

NIDR RESEARCH SUCCESSES

Mr. PORTER. Dr. Slavkin, what personal experiences in mass media do you bring to your Institute to help spread the message of successes of scientific research?

Dr. SLAVKIN. It is a pleasure to respond. In the course of my experiences living in an urban setting in Los Angeles, it became very clear that all of us interested in biomedical research or health, whether it be medical or dental, needed a society that would be mathematically, scientifically and health literate. The opportunity presented itself through KCET, the local PBS station in Los Angeles, to work on a number of programs, "Why In The World" was one, "A Lifetime of Change" was another, which were designed to basically excite and stimulate and educate and guide the intellectual development of young people, focusing on audiences that would be forming minds—third grade, fourth grade, fifth grade, young people who are at a stage where they either buy into math, science, health, literacy, or they take a different direction. I think that the use of television, the era that we live in, has a profound impact not so much in cognitive transfer, but in behavioral attitudes.

I've had a chance to watch two of the recent NIH programs through Maryland Public Television. And I thought that they were very well done. And it seems that this area is an excellent beginning. The downside, from my point of view, is I think we need to reach a much larger audience than the individuals who tune in on PBS.

I hope there will be ways of empowering more teachers, more people who influence children, to have a larger impact in this country, especially inner city people who don't have access to health care, people who are often described as historically underrepresented minorities. That is a population that often carries a disproportionate amount of the disease burden. And we need to invest in how to motivate those populations to basically have a larger stake in science, mathematics and health literacy.

Mr. PORTER. Are you aware of the program and work of Bill Curtis of Chicago in regards to science education?

Dr. SLAVKIN. Yes.

Mr. PORTER. Could you comment on that?

Dr. SLAVKIN. I've only seen the work in little video clips. There have been five-minute clips that were reviewed in Los Angeles for possibly using that material in the LA Unified School District. I believe that several schools are piloting some of his material.

Mr. PORTER. I know Bill Curtis very well personally, and have worked with him on human rights and environmental issues both. And I thought it was a very exciting endeavor to try to motivate young people to become interested in science at the age when you might catch them and reach them with that kind of understanding.

Dr. VARMUS, you taught a class at Anacostia School this week. What was that about? Tell us about that.

Dr. VARMUS. That was part of a series that the NIH has been running for some years called the Mini-Med School. We've given the course in Bethesda, we've given it here on Capitol Hill. This year, with the sponsorship of the American Association of Medical

Colleges, we've been giving the course at the Ballou High School, where there is, in addition to a large high school, an academy for students from the area who are interested in math and science.

On Wednesday evening Tony Fauci and I gave lectures respectively on AIDS and cancer. The audience of about 250 people was large and enthusiastic and the questions were remarkable. I stopped about a quarter of the way through my talk for questions, and there must have been 40 hands up. I watched people suddenly understanding the confrontations they had had with cancer through their friends or their own families.

Shortly into my talk, a 10 year old boy got up and asked, in a very articulate, confident voice, about his father who had died of stomach cancer: what were his chances of dying of stomach cancer? Another woman asked about a friend of hers who had died of breast cancer, and she suddenly understood what metastasis must mean, having heard an explanation.

I found it a riveting and extremely interesting experiment, which I hope we can repeat elsewhere in Washington.

ADMINISTRATIVE STREAMLINING

Mr. PORTER. Dr. Grady, as a small institute with resource constraints, you seem to be a natural candidate for using the service centers set up by various larger institutes. To what extent do you take advantage of these arrangements, and what savings do you foresee for your institute as a result?

Dr. GRADY. Well, we do take advantage of several of the opportunities on campus for using facilities. The service centers are just now becoming something that the NIH has available. We will, for example, probably use the service center in contracts where we have a small program or committee management.

More to the point, we are also sharing other functions with institutes. For example, we share an EEO officer position with the Deafness Institute and we also share our personnel officer with the National Cancer Research Resources. We do share some of these functions in order to maximize our funds available.

Staff are also engaging in cross-training so that our personnel can share workloads with each other. And we have de-layered the Institute in the sense that where we had many small branches, we now have fewer but larger branches. So we're trying to deal in a very creative way with the changes in the Government and still facilitate science and promote the research process.

SYNTHETIC CARTILAGE

Mr. PORTER. Thank you, Dr. Grady.

Dr. KATZ, I understand that some biotechnology firms are working on the development of synthetic cartilage substances to treat the breakdown of the joint associated with arthritis. Does this have promise as a therapy for this disease?

Dr. KATZ. Well, if I can qualify my statement with a potential, yes. At this point, there's very little scientific base that would account for many of the claims that are being made. As you know, one of the techniques that's being used is the removal of some cartilage from an individual. That cartilage is then grown in culture

and re-injected into a defective joint, usually in a patient with osteoarthritis.

There have been many claims made, but the scientific basis for those claims is questionable at this point. First, one would need to follow the patient and see what clinical benefit there is in a well-controlled study; and second, one would need to follow the fate of the cells that are reinjected to learn if they survive. So there are many, many questions as to that new therapeutic intervention.

ALZHEIMER'S DISEASE RESEARCH

Mr. PORTER. Dr. Hodes, some of the researchers in the ApoE camp of Alzheimer's research charge that the peer review process is dominated by those in the amyloid camp who favor their own type of research, even though the ApoE approach is more promising. How do you respond to these criticisms?

Dr. HODES. I think they probably reflect a fairly common phenomenon in areas of exciting science where there are different perspectives, different models. In this case, I think that there has been a growing interaction and communication between those who have appreciated the potential importance of ApoE and those who have appreciated the potential importance of amyloid. In fact, some of the more interesting studies of late have shown that the ApoE variants, which can represent either risk factors or potential protective factors against Alzheimer's, differ in their ability to interact with amyloid.

I think the real construction of the state of the science is that ApoE and amyloid are not competitors as candidates for risk factors or intermediates in the process of Alzheimer's, but are among the undoubtedly complex genetic products which are interacting in the process of that disease. I think in scientific meetings, certainly at the level of peer review and funding, that growing enlightenment is dominating.

TREATMENT FOR TMJ DISORDERS

Mr. PORTER. Thank you.

Dr. Slavkin, in past hearings, we've discussed tempomandibular jaw pain and the controversy associated with previously prescribed treatments of surgical implants. We understand that now the recommended therapy is, less is more, no surgery, some physical therapy, and over the counter pain killers. How did the recommended treatment come full circle to such a modest intervention, and did the aggressive surgical option ever undergo an efficacy review before it was adopted?

Dr. SLAVKIN. As you well appreciate, much of this happened before I came to Bethesda. Several thousand years ago, in the genesis of medicine, the major principle has been "do no harm." I think at a certain stage in history, people thought that by surgically removing condyles and putting in various kinds of implant materials, it was assumed, without scientific rigor, that this might be a solution to the problem. Much of that clearly has failed. We have too many thousands of people with failed implants. That is of historical interest, but also at the moment, those people are still alive and need to be cared for and looked after.

In terms of current thinking, as I mentioned all too briefly in my opening comments, the clear etiology and the clear pathogenesis of temporomandibular joints remains to be discovered. We're having a conference on the NIH campus starting Monday, where so far 1,400 people from around the country have signed up to come. And we're bringing together people who are clinicians, the patient groups, various medical and dental device people, various pharmaceutical companies, biotech companies, Food and Drug Administration people, to come together and collectively essentially take a consensus view of what are the issues and what are the recommendations.

Also what we've done is put out a Request for Applications, and we got a very nice response from an investigator-initiated RO1 point of view to do more fundamental highly original science on the etiology and pathogenesis of these diseases. So at the moment, it isn't an official policy, but there's a climate that people are saying, until more information is known, aggressive treatments seem inappropriate.

NURSING AND CLINICAL ETHICS

Mr. PORTER. Dr. Grady, your institute has established a new clinical ethics program focusing on decision making about participating in genetic studies and clinical trials. I would imagine that nurses are often in the front lines of assisting patients with these decisions. Is the main focus of your work the development of guidelines to deal with patients, or are you studying techniques for recruiting patients into genetic studies?

Dr. GRADY. Actually, you're correct that nurses are very involved in both phases of this process. And although we ultimately will be expecting to be doing both, right now we are concentrating on the decision making process, and the aspects of being tested or not being tested. We are also collaborating with the clinical center and their ethics component, as well as the Genome Center. We are planning to be a part of this long term process and to guide patients in these very difficult decisions, as the information unfolds from the genetic discoveries.

REPETITIVE MOTION INJURIES

Mr. PORTER. Thank you, Dr. Grady.

Dr. KATZ, what is the state of the science on repetitive motion injuries? Do we know enough scientifically for the Federal Government to be promulgating ergonomic standards?

Dr. KATZ. Not yet. Unfortunately, we are not at that stage where we can promulgate certain suggestions in terms of what we should do to treat patients with repetitive motion disorders. The magnitude of the problem is that 2 million Americans have carpal tunnel syndrome, and 4 million Americans have tendonitis of one type or another, for which about 100,000 surgical procedures a year have been performed, according to the Bureau of Labor Statistics, in 1992.

There has been research focusing on repetitive motion disorders in terms of where it is occurring, the chronic microtrauma, and the over-use of certain muscle systems and certain tendons. We had a workshop at the end of 1994 collecting together ergonomics experts, scientists, orthopedic surgeons, and rheumatologists, to look into

this particular question and we're now addressing the question of mechanisms, diagnosis, therapy and prevention in this area. But we are a long way away from knowing the best medical management of repetitive motion disorders.

There have been certain suggestion proposed by the American Academy of Orthopedic Surgeons, as to how one can perform certain exercises during one's daily activities to try to decrease these problems. But those studies are not really based on any good scientific data.

Mr. PORTER. What kind of interface do you have with the National Institute on Occupational Safety and Health on issues like this?

Dr. KATZ. We have just recruited an orthopedic surgeon to be one of our program directors in the orthopedics department to address these particular issues. He comes from the Agency for Health Care Policy and Research and he's had a lot of interaction with NIOSH. So we think that interaction will be facilitated by the appointment of Dr. Panagis to our staff.

Mr. PORTER. But do you have discussions with them in this area? Do you work with them directly on—

Dr. KATZ. We do work with them directly on certain issues. For example, we recently had a conference with them on an irritant contact dermatitis. But I will provide for the record what interactions have occurred between the Institute and NIOSH with regard to repetitive motion disorders.

[The information follows:]

INTERACTIONS BETWEEN NIAMS AND NIOSH CONCERNING REPETITIVE MOTION DISORDERS

NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and CDC's National Institute of Occupational Safety and Health (NIOSH) have had fruitful coordination of research efforts in the past and are continuing to work together to plan future research endeavors. Some examples are provided:

1. In 1994, NIOSH senior scientist Marilyn A. Fingerhut was appointed as a member of the Arthritis and Musculoskeletal Diseases Interagency Coordinating Committee (AMDICC) in addition to the CDC member who had represented NIOSH along with other CDC centers in earlier years. The AMDICC is chaired by the Director of NIAMS and was established by the Public Health Service Act to improve all Federal activities related to arthritis and musculoskeletal diseases. It meets quarterly and produces an annual report to review current agency initiatives, and to identify promising research opportunities and activities that would benefit from interagency collaboration. Dr. Fingerhut has served to connect the researchers in NIOSH with the AMDICC activities.
2. On June 20-22, 1994, a workshop was held on the topic of Repetitive Motion Disorders of the Upper Extremity. This workshop was sponsored by NIAMS, NIOSH, the National Center for Medical Rehabilitation Research of the National Institute of Child Health and Human Development (NICHD), the Orthopaedic Research and Education Foundation, the Center for VDT and Health Research, and the Public Health Service Advisory Committee on Employment of Persons with Disabilities. A group of leading basic and clinical scientists gathered to discuss the state of knowledge and directions for future research in this field.

In the following year, a publication summarizing the presentations was released by the American Academy of Orthopaedic Surgeons. In addition to the presentations, this book contained a long list of recommendations/directions for future research. These included:

- The need for improved epidemiological studies, better surveillance systems, and better diagnostic tools;
- The need for development of better methods to measure the biologic, biomechanical, and biochemical changes in soft tissues subjected to loads, to better understand the physiology of injury, and to understand the healing process;
- The need for development of animal models to better understand these processes;

- The need for developing criteria to distinguish between painful musculoskeletal syndromes having no physical findings and those with a structural mechanism;
- The need for determining clinical indicators of muscle dysfunction;
- The need to determine the clinical management of repetitive motion nerve injury;
- The need to conduct studies on the diagnosis of repetitive motion disorders;
- The need to establish improved measures of functional capacity;
- The need to conduct studies on therapeutic and rehabilitative interventions; and
- The need to determine which work and recreational activities are safe following therapy.

3. In February 1996, the NIAMS participated in developing and implementing the National Occupational Research Agenda. The Agenda, created by more than 500 organizations, agencies, and individuals working with NIOSH, identified 21 priority research areas in occupational safety and health for focused and coordinated efforts during the next decade, with particular emphasis on intervention research. Two priority areas are low back disorders and musculoskeletal disorders of the upper extremities.

Mr. PORTER. Are you aware that the Occupational Safety and Health Administration has drawn up ergonomic standards that they were about to promulgate on repetitive motion injuries?

Dr. KATZ. I am not.

Mr. PORTER. You're not?

Dr. KATZ. I'm a new kid on the block.

Mr. PORTER. I wish Mr. Bonilla was here, because he has taken a very strong position in opposition to their promulgating such regulations at this point in time. And if I read what you said correctly, you've just confirmed that the science is not yet complete or there.

Dr. KATZ. The epidemiology isn't there to start with.

DEMOGRAPHIC RESEARCH

Mr. PORTER. Yes. I will certainly pass that on to him. This was an issue as recent as yesterday, as part of the Omnibus Appropriations Bill, where we originally had language in the House appropriation that would have put those regulations on hold.

Dr. Hodes, I've had a long interest in the demographic research your Institute supports. Are there new findings in demographic research that you can report from the past year?

Dr. HODES. One of the most striking reports in the past year, which I included in the introductory comments, is what has been called a compression of disability, the decrease in disability rates. Among some of the other findings of interest are those which have dealt with mortality and health life span across components of our society.

For example, demographic studies resulting from NIH supported research, in collaboration with the Bureau of Census and other Federal agencies, have identified that there are differences of approximately seven years in males and females in the total life expectancy between whites and blacks, white men and women having about a seven year greater life expectancy than blacks. If one looks at life expectancy from age 85 on, there are essentially no differences in this regard.

If one looks more closely still, rather than concluding there are simply no differences in health status of whites and blacks, it can be seen that the rates of cardiovascular disease in blacks, men and women, tend to be lower than whites after age 85, whereas cancer increases. These data have important implications for research that ought to be directed at specific components of society.

Another important set of studies ongoing are the Health and Retirement Survey and the Asset and Health Dynamics Among the Oldest Old (AHEAD) study. These studies are examining the attitudes and health status of Americans over the transition of retirement age and into later years. The baseline survey has been completed and is now at a stage of extensive investigation and data analysis by multiple NIA supported investigators. This study demonstrated important relationships between wealth and overall health status.

Now, as was the case with many demographic and epidemiologic observations, it becomes imperative to understand the causal nature of the relationship; that is, whether increased wealth in effect buys or permits better accessibility to health care systems, and so provides better health, or whether decreased wealth is the result

of poor health and its concomitants. These very provocative examples of demographic findings will lead to research that will have important implications for health and social care directed at older Americans.

ALZHEIMER'S DISEASE RESEARCH FUNDING

Mr. PORTER. Can I ask a quick follow up on Alzheimer's research? In addition to the investment of NIH, how much is spent by non-profit groups, such as the Alzheimer's Association and the Fisher and Dana Foundations on Alzheimer's research?

Dr. HODES. I do not have available precise figures on DHHS and non-Federal funding. The total expenditures by NIA on an annual basis is estimated at approximately \$220 million per year. This is about 70 percent of the NIH total, which is therefore over \$300 million across institutes which support Alzheimer's research. But I'd certainly be happy to provide for the record the investment and contributions by DHHS and non-Federal organizations.

Mr. PORTER. Thank you, I'd appreciate that.

[The information follows:]

FUNDING FOR ALZHEIMER'S DISEASE RESEARCH

For FY 1995, total reported funding levels related to Alzheimer's disease (AD) were \$304.0 million for the entire Department of Health and Human Services (HHS), of which \$296.7 million were reported by the National Institutes of Health (NIH). Of this, \$215.0 million was spent by the National Institute on Aging (NIA). Under the FY 1997 President's budget request, projected AD spending for HHS as a whole is \$316.8 million, a 4.2% increase over FY 1995 levels; and \$314.2 million for NIH, a 5.9% increase over FY 1995. NIA spending on AD research is expected to be \$227.0 million in FY 1997, a 5.6% increase over FY 1995. Attached is a table showing total HHS spending on AD for FYs 1995-1997.

There are no available data on total funding for AD research by non-profit organizations. However, the following are believed to be the primary funders of AD research. The Alzheimer's Association has estimated that it will spend about \$7.8 million in 1996; the Fisher Foundation reported that over the last five years, it has spent approximately \$10 million; and the American Health Assistance Foundation has spent a reported \$3 million in 1994. Although the Dana Foundation reported that it does not support research on Alzheimer's disease per se, it has funded approximately \$12 million over the last three years for research on neurological disease and memory loss associated with older persons.

ALZHEIMER'S DISEASE

Budget Authority
(Dollars in Thousands)

	FY 1995	FY 1996	FY 1997
Health Resources & Services			
Administration	\$4,959	\$3,993 1/	2/
Centers for Disease Control and Prevention	40	40	40
<u>National Institutes of Health</u>			
NCI	306	306	306
NHLBI	963	1,000	1,025
NIDR	—	—	—
NIDDK	953	990	1,000
NINDS	45,871	47,717	48,563
NIAID	0	0	0
NICHD	425	500	500
NEI	957	1,004	1,020
NIEHS	822	855	874
NIA	214,962	223,000	227,000
NIAMS	1,156	1,230	1,250
NIDCD	1,311	1,389	1,418
NIMH	24,308	25,701	26,128
NIAAA	231	200	200
NCRR	1,276	1,415	1,415
NINR	3,145	3,350	3,400
FIC	55	60	60
National Institutes of Health	296,741	308,717	314,159
Substance Abuse & Mental Health Services Administration	—	—	—
Agency for Health Care Policy & Research	250	500	250
Subtotal, L/HHS	301,990	313,250	314,449
Health Care Financing Administration	1,700	1,900	2,100
Administration on Aging	300	300	300
Total Alzheimer's	303,990	315,450	316,849

1/ Estimate - Alzheimer's program included in cluster for Programs for Special Populations

2/ No specific amount - Alzheimer's program included in cluster Programs for Special Populations.

CLEFT LIP AND PALATE RESEARCH

Mr. PORTER. Dr. Slavkin, you mentioned in your opening testimony when you were talking about cleft lip and palate, collaboration, or at least some interface with research from China. Could you tell us more about that, and how extensive their research efforts are in areas of direct concern to you?

Dr. SLAVKIN. About 18 years ago, there was a very interesting epidemiological study done in Hawaii which first made the observation that the frequency of cleft lip and cleft palate is much higher in Asian peoples than peoples in other parts of the world. That had never been revisited on a large population basis.

And so approximately three or four years ago, a group of scientists here in this country, supported by the National Institute of Dental Research, began an epidemiological study in partnership with China and based in Shanghai.

These investigations are attempting to define gene linkage to determine the candidate genes that might be responsible for this very high frequency of facial clefting in China. It's almost double what it is in other parts of the world. That study has maybe five or six publications that are already in the literature. I think that, within the next 18 months, the study should culminate in a linkage for candidate genes found in mainland China.

INTERNATIONAL RESEARCH COLLABORATION

Mr. PORTER. Perhaps I will ask this question of Dr. Varmus: does China have an institutional structure similar to NIH or at least organized at the national level?

Dr. VARMUS. There are scientific institutes there, at least one of which I visited. They have institutes for specific research, for example, genetics and immunology in some of the major cities. The amount being spent on medical research is of course considerably less than in this country. But we do now have significant contacts with those institutes, and a number of collaborative projects through a number of institutes in China.

Mr. PORTER. I've been very interested in what Dr. Klausner is doing in the Middle East, and the need to find ways of collaborating and interfacing with some of the repressive societies on matters of common interest that take us out of the political sphere and get us working on something positive. And that's the reason I asked the question.

Dr. VARMUS. Well, as you know, we're interested in that as well. In fact, this afternoon, a number of scientists from Africa will be joining scientists and administrators from Great Britain and France to discuss the initiative we mentioned here briefly, to try to confront malaria in Africa in a more efficient fashion, through some collaborative arrangements. So we believe there, too, where there has been considerable political disruption, that we can work together through health to try to advance a number of agendas.

BASIC NURSING RESEARCH

Mr. PORTER. That's wonderful. I am glad to hear that.

Dr. Grady, I was interested to see that your testimony highlighted some basic research efforts. I thought the Nursing Institute

focused more on clinical applications and health services research. Does this represent a change in emphasis for you?

Dr. GRADY. We fund up to about 10 percent of basic research in our Institute. So the bulk is still clinical. The type of basic research that we study is research that addresses clinical problems. A really good example of completed research is an animal laboratory study that actually started in combination with NIAMS in animal models of immobilization.

The changes in muscle were studied in terms of immobilization followed by exercises and activity in those immobilized muscle areas. Changes in recovery were seen. Then that study was carried into the clinical area by the post-doc students of the nurse researchers, who had done the laboratory study. That study now is being carried on clinically. This also stimulated some interest from the National Aeronautics and Space Administration and we now have intra-government support.

That's an example of one of the areas that we're working on. Another area related to Alzheimer's disease includes a study in animals with brain lesions that are analogous to Alzheimer's patients. The researchers are using cues for direction finding in an attempt to identify parameters that may be used clinically to guide Alzheimer's patients who tend to become lost and to wander. What we're doing is really a study from the basic to the bedside. The issues that we're addressing are those which are more immediately translated into clinical settings.

NURSING RESEARCH PLANNING

Mr. PORTER. Now, I'll ask the larger question. Are you still operating under the strategic plan formulated by your predecessors, or have you determined that the Institute needs a newer or broader focus?

Dr. GRADY. There was a National Nursing Research Agenda that was a very elaborate planning process that was put in place when the Institute was formed as a center. That had two five year segments. The second five year segment is up within the next two years. The priorities that were identified were those of HIV-AIDS and also of cognitive dysfunction. Those are two areas which happen to be very timely from a research point of view and also have a great deal of impact from a standpoint of our population and the nation.

So we are going forward with those initiatives. However, we do appreciate in times of fiscal constraint that the planning process may need to be less elaborate. What we are looking at now is having smaller work groups convene at national meetings, and also using our council more actively. We have convened two workgroups this year, one on opportunities in nursing issues in the environment, and one on nursing in genetics.

We are using the base that has been built by the extramural investigative community as a result of this very elaborate planning process. We're building on that using small advisory groups, using our large council, and also taking advantage of the scientific opportunities as they emerge from the other areas across the institutes and across the country.

PANEL FORMAT

Mr. PORTER. Dr. Katz, Dr. Hodes, Dr. Slavkin, Dr. Grady, and of course, Dr. Varmus, let me thank each one of you for your participation in the panel and answering all the questions that I've posed this morning. I will, Dr. Varmus, ask you if you would obtain for us whatever comments members of this panel and the Monday panel want to make about the format, which is different than we've done before, and see if we can't get some impressions as to what you feel about it.

[The information follows:]

The comments that follow reflect ICD input relative to the use of panel formats for presenting the NIH budget request:

Views on Panel Format for Hearings

Dr. Harold Varmus, Director, National Institutes of Health

The National Institutes of Health (NIH) had two panel presentations. I thought the format worked well in the panel of April 26, primarily because the questions tended to elicit group discussion. Little was gained by the panel format on April 22 when each Director was separately questioned, so that the strong collaborative interactions among some of the neuroscience institutes did not emerge. NIH would need another trial of the panel method in the presence of a committee of more than one or two members to make any solid judgment.

PANEL 1

Dr. Zach Hall, Director, National Institute of Neurological Disorders and Stroke

We appreciated the opportunity to comment on the effectiveness of using panels for this year's hearings. We found that the opportunity to appear with other institutes concerned with brain research helped to underscore some of the common themes in neuroscience, in keeping with the collaborative efforts we have undertaken at NIH. However, we believe that individual presentations provide more opportunity for the institutes to highlight the broad spectrum of advances and initiatives within their purview. They really give a sense of what makes each institute unique in terms of disease emphasis, type of science supported, and interactions with the scientific community and the public.

Individual presentations also provide a better forum for the Committee to explore issues, questions, and concerns. While it is always possible for members to ask questions for the record, the interchange that occurs at a hearing allows for clarification and follow-up in a way that written questions do not.

As the chairman noted, the panel format appears to work best when only a few members are present. That certainly appeared to be the case this year, in contrast to two years ago when we testified with two other institutes and there were more members asking questions. NIH is fortunate that so many members make the effort to attend the hearings; if the schedule permits, it would seem best to use a format that facilitates questions and discussion.

Dr. Steven E. Hyman, Director, National Institute of Mental Health

In my opinion, the panel format idea should be abandoned as a failed experiment. I believe that it worked to some degree for our panel, but only because most of the Committee members were absent. Even so, I found that the panel approach had the effect of creating some degree of confusion regarding the missions and programs of the various Institutes and also negatively impacted on the ability of the Institute Directors to articulate both their priorities and visions of the future.

Dr. Alan Leshner, Director, National Institute on Drug Abuse

The format seemed to lack focus. Although I thought it worked well for the authorization process, where there was a clear single topic, I felt here we had confusing purposes and made general points while still trying to articulate each of our uniqueness. It was too much to ask of this format. And if there were multiple members present, it would have been worse. I suggest we evaluate other approaches in the future if we need to compress time.

Dr. Enoch Gordis, Director, National Institute on Alcohol Abuse and Alcoholism

While our panel gave some opportunity for presenting common approaches, it did lend itself easily to the questions about merging Institutes. This was the first time that this matter has come up in my nine years of giving testimony.

In addition, the portfolio of each Institute is certainly rich enough to fill the more convention 45 or 60-minute solo exchange. In sum, I believe that the traditional approach is preferable.

PANEL 2

Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

The panel format can be useful to highlight some of the areas of collaboration between different ICDs, but there is a lot of value to the single ICD approach. The single-ICD approach allows each institute to highlight their areas in an important forum and to have the stage to themselves for a short time. If the decision is made to continue panel-type hearings we would suggest the following:

- 1) Rotate participation on the panels so that ICDs on a panel this year would not be on one next year. In this manner, the single -ICD approach gets shared with everyone.
- 2) Change the make-up of each panel. In other words, do not have the same ICDs on the same panel each time. This would allow NIH to emphasize different "themes."
- 3) A panel format will work best if we know well in advance of the theme of the panel so the appropriate questions can be prepared to give each ICD comparable visibility and give us time to coordinate responses.

Dr. Richard Hodes, Director, National Institute on Aging

The panel format for this year's budget hearing which included National Institute on Aging (NIA), National Institute of Dental Research (NIDR), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and National Institute of Nursing Research (NINR) proved to be a very useful exercise, and I am privileged to have represented NIA in the panel. Given that each of these four organizations has different research foci and varying missions, the panel format provided an excellent opportunity for us to demonstrate the extent to which the individual Institutes collaborate on common research interests and on critical biomedical and behavioral issues.

I believe that at the close of our hearings, you noted that the panel format worked very well and that it was unfortunate that other members had not been able to be present to witness the positive excitement conveyed by the Directors. However, I am concerned that in the panel format topics which are of major interest to Congress and to the public may not receive the attention which they merit if they fall within the purview of one institute, but do not qualify as cross-cutting areas of interest or emphasis for all institutes in panel.

At this year's hearing, discussion of one area of particular interest for NIA, Alzheimer's disease, was less comprehensive at this year's hearing than in the past since it was not an area common to all Institutes present. However, I believe that a reasonable balance between panel questions and Institute specific questions did exist this year, and that all interests can continue to be served if a block of time is devoted for Institute specific questions when the panel format is utilized.

Dr. Harold Slavkin, Director, National Institute of Dental Research

Upon reflection, the "experimental panel design" went quite well with Mr. Porter as the sole source of questions. He was extremely "positive" to each of us and provided a very comfortable environment. That comfort clearly reflected a fine collegiate relationship among the four of us.

More critically, if there were many members in attendance, and if each were to pursue their line of questioning, I sense this format would not be successful. Balance would be lost and a sense of real analysis of each ICD might also be lost. As a smaller ICD, this is of particular concern.

Second, I would suggest that if the Panel approach is to be continued, rearrangement of the panels by different combinations of ICDs would be a very good approach. For example, NIDR could combine with other ICDs around the themes of neuroscience, cancer, birth defects and/or chronic disabling diseases. By changing the arrangements, our NIH could transmit a true sense of trans-NIH interaction at many levels of activity.

Finally, my preference would be to have the House Appropriations hearings with individual ICDs. This format optimizes a focus on each ICD for a modest period of time and provides the uniqueness and creativity of each ICD to be clearly expressed and analyzed. The format of four on a panel did not provide that sense of appraisal or participation from my point of view.

I hope these concerns will be of some value as we shape the formats for the future. Thanks for the opportunity to provide some feedback.

Dr. Patricia Grady, Director, National Institute of Nursing Research

The panel approach worked well, particularly with Mr. Porter as the sole questioner. He was even handed, assuring that each institute had the chance to speak for about the same length of time. The dual approach of asking one question for all to answer, then specific questions of each institute, achieved the goal of showcasing areas of mutual interest, collaboration and individual perspectives on research problems--and the special missions and priorities of each institute.

Mr. PORTER. And this also, of course, completes all of our Institute testimony for NIH. I'm very anxious to have the members come out and visit the Bethesda campus, and appreciate your cooperation in arranging that.

And I also, if we have the opportunity and we have not discussed this, but I would again like to see if we can bring a panel of Nobel laureates in to spend a day after we complete our formal hearings with the subcommittee. I think they would find, as I always do, that to be a fascinating and interesting day as well.

Dr. VARMUS. We're happy to do all those things, Mr. Porter. I just want to conclude by saying that I appreciated today's panel. To borrow an earlier metaphor, it has allowed us to explore the ways in which institutes, like ApoE and amyloid constituents, can be not competitive but cooperative and interactive. I also appreciate the very high level at which you've run these hearings in the last week. It's been enjoyable for me to watch them.

Thank you.

Mr. PORTER. Thank you all very much. The subcommittee will stand in recess until 10:00 a.m. on Tuesday.

[The following questions were submitted to be answered for the record:]

**NATIONAL INSTITUTE OF ARTHRITIS AND
MUSCULOSKELETAL AND SKIN DISEASES****PUBLIC EDUCATION**

Mr. Porter: How much does your 1997 budget include for public education efforts?

Dr. Katz: The FY 1997 estimate for public education activities within the NIAMS is \$1.7 million.

FIBROMYALGIA

Mr. Porter: Last year the Subcommittee recommended that NIAMS collaborate with other institutes on research the fibromyalgia syndrome. What accomplishments have been made in this area and what other plans for Institute collaboration do you have in the future?

Dr. Katz: In a very promising advance in research on fibromyalgia, NIAMS-supported investigators used a new imaging technique to determine if cerebral blood flow is abnormal in women with this disorder. Women with fibromyalgia and normal controls underwent the brain imaging procedure, assessment of pain thresholds, and psychological evaluation. The researchers found that women with fibromyalgia display significantly lower pain thresholds and significantly higher anxiety and depression scores. With regard to the brain scan, patients with fibromyalgia were found to have significantly lower blood flow. These findings suggest that structures in the brain involved in pain perception may have a functional abnormality that accounts in part for lower pain thresholds. These findings could help researchers target better intervention for patients with fibromyalgia. In addition, the NIAMS has taken the lead in planning a workshop on fibromyalgia on July 16-17, 1996. We are collaborating with other Institutes, fibromyalgia researchers, neuroscientists, endocrinologists, and other investigators nationwide. The goals of this workshop are to assess progress in our understanding of fibromyalgia, to identify new directions in research on fibromyalgia, and to stimulate increased interest in this field.

Mr. Porter: Two years ago the Subcommittee recommended that NIAMS consider establishing grants to train new investigators in fibromyalgia. How are you progressing on this front?

Dr. Katz: We are continually trying to generate investigator interest in studying various aspects of Fibromyalgia. In 1994, the NIAMS issued a Request for Applications that resulted in funding for five investigators who were all new to this field. In 1996, one additional new investigator has been funded for research on fibromyalgia. In addition, the workshop on fibromyalgia that is planned for July 16-17, 1996, will bring a number of investigators from related fields together with established scientists in fibromyalgia for multidisciplinary discussions. This can be expected to increase the number of new investigators conducting research on fibromyalgia.

DISEASE DOLLARS

Mr. Porter: Identify 1995-97 spending for the following diseases: osteoporosis, rheumatoid arthritis, osteoarthritis, lupus, lyme disease, epidermolysis bullosa, ichthyosis, psoriasis, alopecia, scleroderma, osteogenesis imperfecta, Marfan's syndrome, and fibromyalgia.

Dr. Katz: Funding for these diseases in FYs 1995 - 1997 is as follows:

	FY 1995 <u>Actual</u>	FY 1996 <u>Estimate</u>	FY 1997 <u>Estimate</u>
Alopecia	\$ 129,000	\$ 135,000	\$ 140,000
Epidermolysis Bullosa	6,740,000	7,300,000	7,440,000
Fibromyalgia	1,464,000	1,545,000	1,560,000
Ichthyosis	5,133,000	5,360,000	5,530,000
Lupus	21,652,000	22,815,000	23,360,000
Lyme Disease	2,462,000	2,585,000	2,650,000
Marfan's Syndrome	938,000	980,000	1,010,000
Osteoarthritis	15,233,000	16,060,000	16,280,000
Osteogenesis Imperfecta	1,115,000	1,170,000	1,200,000
Osteoporosis & Related Diseases	45,775,000	47,990,000	49,245,000
Psoriasis	4,722,000	4,990,000	5,125,000
Rheumatoid Arthritis	17,271,000	18,270,000	18,360,000
Scleroderma	2,689,000	2,890,000	2,935,000

RESEARCH CENTERS

Mr. Porter: Identify the number, types and subject matter of the research centers supported in 1995?

Dr. Katz: The NIAMS supported 30 research centers in FY 1995. These include 14 Multipurpose Arthritis and Musculoskeletal Diseases Centers (MACs), 9 Specialized Centers for Research (SCORs), 6 Skin Disease Research Core Centers (CORE), and 1 Juvenile Rheumatic Diseases Research Center Planning Grant. Included in the nine SCORs are 4 in rheumatoid arthritis, 2 in osteoporosis, 2 in systemic lupus erythematosus (SLE), and 1 in osteoarthritis.

FIBROMYALGIA

Mr. Porter: Dr. Katz, you are having a consensus conference on fibromyalgia to stimulate research interest in the field. How would you characterize the quality and volume of research applications you presently receive in this area?

Dr. Katz: The meeting planned for July 16-17, 1996, is actually not a consensus conference, but a working group on fibromyalgia. While the previous workshop in May 1993 provided an overview of the whole field of fibromyalgia, this workshop has a particular focus. The goal of this workshop is to stimulate consideration of the basic science of chronic pain, sleep, neuroendocrine function, and circadian rhythms -- all traits that are altered in fibromyalgia. The workshop will include neuroscientists, endocrinologists, and sleep researchers who will share the latest research advances in these fields that are relevant to fibromyalgia researchers. Each session will be led by fibromyalgia researchers who are well known in this field. The workshop is being co-sponsored by the NIAMS, the NIH Office of Research on Women's Health, and the National Institute on Nursing Research. In addition, staff from the National Institute of Child Health and Human Development are participating in the workshop and the invitation to participate in this workshop will be sent to a wide array of investigators from multiple Institutes across the NIH campus.

Mr. Porter: What are your plans for expanding fibromyalgia research in the future?

Dr. Katz: The NIAMS will continue to encourage research on fibromyalgia and will use recommendations from the scientific workshop on fibromyalgia on July 16-17, 1996, to identify areas of research where the scientific opportunity is greatest for increased emphasis and support. The NIAMS remains committed to supporting high quality research to address the many basic and clinical questions remaining on this disorder that is so challenging for patients and their families.

LOW BACK PAIN

Mr. Bonilla: In testimony presented before the Committee, we learned that your Institute, in conjunction with the American Academy of Orthopaedic Surgeons, sponsored a symposium in November 1995 addressing "New Horizons in Low Back Pain." What major recommendations resulted from the symposium?

Dr. Katz: The workshop on low back pain, held in November 1995, was very useful in identifying areas where opportunities are ripe for increased research. Some of the priorities identified by workshop participants included: (1) The need to better define the natural history of idiopathic low back pain, ruptured disc, and spinal stenosis. This would include an attempt to standardize terminology and physical examination methods. (2) The need to better define the role of various diagnostic imaging techniques, to determine the proper timing and sequencing of these studies, and their correlation with clinical findings. (3) The need to better understand the causes of low back pain, ruptured disc, and spinal stenosis, to enhance our diagnostic, treatment, and preventive strategies. (i.e., need for more basic science research--biochemical to animal modeling). and (4) The need for clinical studies to evaluate the effectiveness and outcomes of specific treatment modalities (ranging from physical therapy to spinal manipulation to surgery), and to better define in which patient, and at what time in their disease course, will these treatment effects be optimized. There were frequent citations throughout the meeting of the need for randomized clinical trials. A common theme of all the presenters was the need for increased research efforts in low back pain research.

Mr. Bonilla: Will your Institute fund in FY 1997 any of the recommendations?

Dr. Katz: The NIAMS is launching an important new study that will examine patients with low back pain to determine why some individuals get better in a short time versus those who do not. This type of pain--acute low back pain--has traditionally been a neglected area of study. By examining factors related to acute low back pain, the researchers hope to be able to provide information that will help physicians more accurately identify those patients who will get better shortly and those that will require prolonged care.

Mr. Bonilla: Are there any major new clinical trials you hope to fund in FY 1997?

Dr. Katz: The NIAMS is currently funding a study on acute low back, as mentioned earlier, and is also supporting a clinical trial on degenerative spondylolisthesis, a back disorder that occurs when one vertebra slips over another. This clinical trial will compare various treatments of degenerative spondylolisthesis to determine which treatments provide optimal pain relief and improve disability. Based on the outcomes of these and other studies, as well as the receipt of promising research applications, we may proceed with other trials designed to examine this serious problem.

REPETITIVE MOTION DISORDERS

Mr. Bonilla: In your view, should OSHA be allowed to expand the definition of an ergonomic injury to include symptoms such as aches and pains and require employers to report those as workplace injuries and illnesses?

Dr. Katz: I think it is important to first clarify the differences between the NIH, NIOSH, and OSHA perspectives. At the NIH, we explore the full range of research in a respective area. That is, we support research from the very basic--cellular and molecular--levels all the way to the patient-oriented clinical applications. In this manner, NIH attempts to generate a knowledge base that will allow researchers to understand the full details of a particular disorder. The focus of NIOSH research, on the other hand, is on the etiology and prevention of illnesses, injuries, and deaths caused by hazards on the job. When NIOSH determines that a sufficient research base exists to indicate a threat to worker health and safety, they may recommend to OSHA that regulations to protect workers be promulgated. This is an important distinction. It may not be necessary to understand the full details of a particular disorder in order to determine that a sufficient knowledge base exists to make recommendations for prevention. My comments reflect the NIH perspective.

With regard to your specific question, I would not expand the definition of an ergonomic injury to include symptoms such as general aches and pains as sole indicators. If there were a standard, the reported conditions/diagnoses should be as exact as possible. This specificity will facilitate illness/injury surveillance and will facilitate subsequent studies for the effectiveness of preventive programs and treatment modalities.

Mr. Bonilla: In your view, if OSHA is allowed to expand the definition of an ergonomic injury to include symptoms such as aches and pains, what will happen to the validity of the information Bureau of Labor Statistics (BLS) relies on to report workplace injuries and illnesses?

Dr. Katz: Although not all states report workplace illnesses/injuries to the BLS, it is one of the most commonly cited references on their occurrence. I believe that the inclusion of these two subjective complaints, as sole indicators, may impair the validity and usefulness of this instrument. Also, as mentioned above, their inclusion may hamper surveillance activities and future studies on the effectiveness of preventive programs and treatment modalities.

Mr. Bonilla: If OSHA's science in the area of ergonomics is not sound, as you stated during your oral testimony, are you aware of any authority which does have the sound science OSHA needs?

Dr. Katz: I am sorry that my response to Mr. Porter was not clear. I did not mean to imply that OSHA's science in the area of ergonomics is not sound, and my comments were not on the specific OSHA draft, but on the more general question of medical management of repetitive motion disorders. The Workshop on Repetitive

Motion Disorders of the Upper Extremity, as mentioned during my testimony, brought together basic scientists and researchers with an interest in these disorders. The conferees recommended the following areas for future research needs: (1) improved definitions of repetitive motion disorders (RMD's); (2) studies to facilitate the diagnosis of RMD's; (3) establish improved measures of functional capacity; (4) conduct studies on therapeutic and rehabilitative interventions; (5) improve and standardize outcomes measures for RMD's; and (6) determine which work and recreational activities are safe following treatment (both conservative and surgical), and when it is most appropriate to do them.

Mr. Bonilla: Can you explain why you do not believe OSHA's science is sound?

Dr. Katz: I am sorry that my response to Mr. Porter was not clear. I did not mean to imply that OSHA's science in the area of ergonomics is not sound, and my comments were not on the specific OSHA draft, but on the more general question of medical management of repetitive motion disorders as mentioned above.

Mr. Bonilla: Has OSHA sought any advice or counsel from NIAMS with regard to ergonomics?

Dr. Katz: To the best of my knowledge, we have not been consulted by OSHA regarding ergonomics. NIAMS does interact with the National Institute for Occupational Safety and Health and participated in the above-mentioned workshop. NIOSH, of course, supports research and surveillance on work-related musculoskeletal disorders. As such, we have historically had programmatic contact with them.

Mr. Bonilla: Do you have an idea as to how long it will take for the scientific foundation OSHA requires to proceed with its ergonomics rulemaking?

Dr. Katz: As stated above, I have reservations that the medical management research base may not be sufficiently developed to institute certain components of a medical management plan. I cannot predict how long it may take to develop the knowledge regarding medical management.

Mr. Bonilla: If the Committee prohibited OSHA from developing or promulgating an ergonomics rule, would this stop NIAMS, NIOSH or the scientific and medical communities from continuing to do more research into the causes of MSDs or RSIs?

Dr. Katz: If the Committee prohibited OSHA from developing or promulgating an ergonomics rule, this would not stop NIAMS, NIOSH, or the scientific and medical communities from continuing to do research in these areas. However, surveillance and reporting data can provide needed epidemiological information that can be integral to further research into the causes of these and other disorders.

Mr. Bonilla: In your view, can OSHA develop an effective ergonomics rule before the scientific and medical communities do more research?

Dr. Katz: I know that more research is needed, but it may not be necessary to understand the full details of a particular disorder to determine that a sufficient knowledge base exists to make recommendations for prevention.

Mr. Bonilla: Does cigarette smoking cause a loss of blood flow to the outer extremities of the hands? If so, does this predispose a person for repetitive strain injuries to the outer extremities of the hand?

Dr. Katz: Nicotine is known to cause vasospasm (or narrowing) of small blood vessels. Following replantation of a severed finger, for example, it is generally recommended that the patient not be exposed to cigarette smoke until the viability of the repaired finger is assured. It is not known whether nicotine predisposes one to repetitive strain injury of the hands. More research is needed before we can answer this question.

Mr. Bonilla: Are there any other personal habits, such as overeating or excess intake of alcohol, that may put a person at increased risk of experiencing musculoskeletal disorders?

Dr. Katz: Excess intake of alcohol and overweight status are factors that can predispose an individual to musculoskeletal disorders. Other possible factors are other concurrent medical conditions, previous history of work illnesses/injuries, and job satisfaction. NIAMS is currently supporting a research project specifically looking at these risk factors as predictors of the development chronic or complicated low back pain in an industrial workforce presenting with low back pain of less than 30 days duration.

Mr. Bonilla: Should complaints of pain without any diagnosis of pathology be considered and recorded as a work-related injury/illness? Why?

Dr. Katz: Subjective complaints of pain without any diagnosis, rarely if ever, are considered in this process. I believe that the inclusion of the subjective complaint of pain, as a sole indicator of illness, without any diagnosis may impair the validity of a surveillance and reporting tool.

FIBROMYALGIA

Mr. Dickey: Dr. Katz, fibromyalgia causes great pain and hardship for many Americans, the majority of them women. What progress can you report from research on fibromyalgia?

Dr. Katz: Fibromyalgia is a very challenging disorder for patients and their families, as well as the physicians who treat them. Fibromyalgia affects women seven times more than men. One of the characteristics of this disorder is specific sites of tenderness and pain in the body. Recently, using a new imaging technique, investigators studied women with fibromyalgia and normal controls who underwent the brain imaging procedure, assessment of pain threshold levels, and psychological evaluation. This research revealed that women with fibromyalgia display significantly lower pain thresholds and significantly higher anxiety and depression scores. On the brain scan, patients with fibromyalgia had significantly lower blood flow, when compared to normal controls. These findings suggest that the structures in the brain involved in pain perception may have abnormal function that contributes to the lower pain thresholds. These findings may help researchers to target better interventions for relief of this debilitating disease.

GENE THERAPY

Mr. Dickey: What is your view of gene therapy as a treatment for diseases in the research areas of your Institute?

Dr. Katz: The ability to replace a gene that is not functioning properly and treat a genetic disease is a very exciting prospect. Scientists and the public have been eager for this type of intervention to succeed. At this point, it seems that the technology must progress a bit further before gene therapy can be a viable, wide spread technique for treating genetic diseases. To encourage research proposals in this area, the NIAMS issued a Request for Proposals, "Gene Therapy for Rheumatic and Skin Diseases," in March 1996, soliciting proposals for advancing the state-of-the-art for gene therapy in the areas in rheumatic and skin diseases. Awards are expected to be made in late September 1996. The scope of this research includes improvement and adaptation of current gene therapy technology, development of new methods to introduce, maintain and regulate gene expression in target organs and cells, production of new reagents for gene therapy, and development of innovative experimental systems to test the feasibility of using gene therapy technologies for the treatment of human rheumatic and skin diseases. Research in this area holds great promise for the future for patients with rheumatic diseases and skin diseases, as well as other diseases outside the research areas of the NIAMS.

RHEUMATOID ARTHRITIS

Mr. Dickey: What progress is being made in understanding rheumatoid arthritis? Are there any new studies that suggest a causative agent?

Dr. Katz: Past research has shown that abnormal immune responses to bacteria are implicated in some rheumatic diseases, but the triggering antigens (substances that, when introduced into the body, are recognized by the immune system as alien) in rheumatoid arthritis were unknown--until recently.

NIAMS-supported researchers discovered that patients with early rheumatoid arthritis showed a strong response to certain bacterial antigens. The researchers believe this response may contribute to the development of rheumatoid arthritis. This finding provides evidence for the first time that a link exists between a bacterial antigen and an abnormal immune response in the joint fluid of patients with early rheumatoid arthritis. The finding could lead to a better understanding of the disease process and to development of new strategies for delaying the progression of this disorder.

OSTEOARTHRITIS

Mr. Riggs: Dr. Katz, the procedure to regenerate and restore tissue has been widely reported in the media. Is your Institute currently conducting studies on this method of restoring tissue?

Dr. Katz: Although we are not currently conducting clinical studies in this area, the Institute is supporting research on the regeneration of tissue. For example, the NIAMS is funding research looking into how connective tissue from rib cartilage can be transplanted into a joint to help replace joint tissue that has degenerated. This research effort may provide techniques that can lead to the reliable repair of human cartilage defects which have been caused by injury or by disorders such as arthritis.

Mr. Riggs: We have heard in testimony that osteoarthritis not only affects the elderly, but has been found in individuals 45 and younger. And because of the high costs to treat this condition, many of the patients become a liability to society. Doctor, will the Institute fund any new clinical trials in this area in FY 1997?

Dr. Katz: The NIAMS currently supports intervention studies aimed at modifying patients' behavior, pain perception and physical activity to cope with osteoarthritis. These and other studies supported by the Institute help to provide additional information that is useful to researchers who may be interested in submitting applications for clinical trials. Based on the outcomes of these studies, and on new research applications submitted, we may fund clinical trials in this area.

TRAUMA AND SPORTS-RELATED INJURIES

Mr. Riggs: Doctor, we understand from testimony that the costs of lost productivity and emergency medical care associated with trauma and sports-related injuries continues to place a tremendous burden on society. Does the Institute have underway any on going activities to educate our citizens of the importance of taking safety precautions?

Dr. Katz: The Institute supports a sports surveillance study whose purpose is to reduce the incidence and severity of sports injuries occurring in youth. As part of this study, coaches are trained to more easily identify injuries so that further, more severe injury can be avoided.

The NIAMS is also aware of a campaign sponsored by the American Academy of Orthopaedic Surgeons called "Play It Safe: Sports". They have developed a packet that includes a poster, a brochure and a number of fact sheets designed to educate the public. This safety information includes topics such as baseball, soccer, football, gymnastics, hockey, and skiing. In addition, new fact sheets are being developed on other topics such as tennis, volleyball, and basketball, for example.

Mr. Riggs: Are there studies being conducted to develop synthetic replacements for muscle, tissue or bone damaged beyond repair as result of trauma?

Dr. Katz: The NIAMS has a long history of supporting research in this area. For example, we have long supported research on total hip replacement. Recently, the NIAMS sponsored a consensus conference on total hip replacement which, among other things, highlighted the need for developing new biomaterials. The Institute has also launched a Program of Excellence in Orthopaedic Biomaterials, and as a result, has funded four new studies in this area.

In other efforts, the NIAMS and the National Institute of Dental Research (NIDR) are undertaking a new initiative to examine the cellular and molecular mechanisms of connective tissue repair. This initiative includes efforts aimed at identifying critical repair functions in different tissues and the biological agents of repair processes, characterizing the molecular mechanisms by which such agents function in repair, and developing techniques for the manipulation of various cell populations to facilitate repair processes.

SYSTEMIC LUPUS ERYTHEMATOSUS

Mr. Stokes: As you know, African Americans are disproportionately impacted by lupus. What progress do you have to report since the Institute last appeared before the subcommittee? To what extent are we closer to unraveling why African Americans have a disproportionately higher prevalence for lupus?

Dr. Katz: Systemic lupus erythematosus (SLE, or lupus) is an autoimmune disease that is three times more common in African Americans than in white Americans, and also tends to be more severe in African Americans. Researchers supported by the NIAMS have identified a gene associated with increased risk of lupus kidney disease in African Americans. Variations in this gene affect the ability of immune cells to remove potentially harmful molecules from the body. This finding is a significant step towards enabling doctors to predict who is at risk for lupus and its complications and to take steps to minimize that risk.

Researchers are also working to identify other genes involved in determining susceptibility to lupus. They have evidence that multiple genes contribute to disease susceptibility, and that no single gene can by itself cause the disease. The NIAMS will continue to place a high priority on research into this serious disorder.

MINORITY RESEARCH INVESTIGATORS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under its purview?

Dr. Katz: On April 16, 1996, the NIAMS sponsored a very effective and well received workshop, "Enhancing Career Development: A Workshop for NIAMS-supported Underrepresented Minority Scientists." It was held the day after our 10th Anniversary of the NIAMS Celebration, a scientific symposium that was attended by participants in the minority meeting. The purposes of the Workshop were to acquaint participants with the opportunities and options open to them in the field of biomedical research; to impart information on applying for research project and career development grants; and to provide an opportunity for networking with NIAMS extramural and intramural staff.

Mr. Stokes: What efforts have your Institute undertaken to educate minorities on opportunities that are available in biomedical research?

Dr. Katz: The NIAMS sponsored a workshop on the NIH campus on April 16, 1996, "Enhancing Career Development: A Workshop for NIAMS-Supported Underrepresented Minority Scientists." This was a very practical, hands-on meeting attended by 32 young minority scientists that included presentations on the career challenges for minority students, presented by Dr. John Ruffin, Associate Director

for Research on Minority Health, NIH; a personal journey in research, in which Dr. Luis Diaz shared his own inspiring story; mentoring and networking in career development; a panel discussion with audience participation with an emphasis on what the minority scientists should be focused on at particular stages in their careers; a session on grantsmanship; and a poster session that included information on grantsmanship, different grants for different career stages, alternate funding sources, the NIAMS Intramural Research Program, the NIAMS priority research areas, and strategies for networking and mentoring. This program proved to be a very good vehicle for informing and mentoring minority scientists.

EPIDERMOLYSIS BULLOSA

Mr. Stokes: How is the Institute utilizing the advances gained from its research in epidermolysis bullosa, a devastating and blistering skin disease to improve the quality of life for patients suffering from the disease?

Dr. Katz: Epidermolysis bullosa represents 20 different forms of rare, hereditary blistering disorders that involve the skin and mucous membranes. Epidermolysis bullosa is a life-long disorder and can cause extreme physical, emotional, and financial hardships for the afflicted patients and their families. Researchers have identified the precise location in skin that is affected by epidermolysis bullosa and the genes that are mutated in the various forms of these diseases. Research results such as these continue to shed light on the genetic origin of the various forms of epidermolysis bullosa and have generated a renewed optimism for altering the course and for improving treatments for these diseases. The NIAMS is continuing to support research on the genetic origins of this disease and to find new treatments for this debilitating skin disorder.

OSTEOARTHRITIS

Mr. Stokes: Osteoarthritis is a leading cause of disability for many Americans. What is the cost of osteoarthritis to the nation?

Dr. Katz: In 1995, the official research journal of the American College of Rheumatology published a detailed report which cited \$64.8 billion as the cost of arthritis in the United States for 1992. This work was supported by the National Arthritis Data Workgroup, which is funded by the NIAMS. I am not aware of research that further details the cost of individual arthritic disorders such as osteoarthritis, rheumatoid arthritis, for example.

Mr. Stokes: I understand that last year the Institute funded a request for applications on osteoarthritis. What do you hope to learn from this initiative?

Dr. Katz: This initiative is designed to examine a broad array of topics that will enhance our understanding of osteoarthritis. Some of these topics include exploration of the genetic basis for some types of osteoarthritis, elucidation of age-

related changes in joint tissues and their role in the development and progression of osteoarthritis, the development of biological markers for osteoarthritis, and investigations into the role and structure of the joint in the development and progression of this disease.

MINORITY HEALTH

Mr. Stokes: For the diseases and disorders that are under the purview of your Institute, where are we now with respect to closing the gap in minority health? Specifically, what progress do you have to report to the subcommittee this year?

Dr. Katz: Lupus is one example of the many diseases within the research mission of NIAMS that affect women and minorities disproportionately. Systemic lupus erythematosus is a multisystem disease that affects women nine times more often than men and lupus is three times more common in African American women than in white women. Lupus is an example of a problem that we address using laboratory or bench science, animal or epidemiologic research, and clinical trials. To address this, we interact closely with our colleagues in the Office of Minority Health as well as the Office of Research on Women's Health. One example of this interaction is our co-funding of the first clinical trial on the safety of estrogens for women with systemic lupus erythematosus. Currently, women with lupus are usually advised not to take any medications with estrogen in the belief that it will worsen their disease or cause problems with blood clotting. We are supporting this study because women with lupus now have limited options for contraception during child bearing years and for hormone replacement therapy during postmenopausal years. The outcomes of this trial are expected to have a significant effect on treatment options, health, and quality of life for patients with lupus.

In addition, striking advances in molecular biology and molecular genetics have dramatically improved the pace of research to identify the genes that contribute to lupus susceptibility, severity, and mortality. On March 1, 1996, scientists reported the identification of a genetic risk factor for lupus kidney disease in African Americans. The NIAMS has also established a registry for patients with lupus as well as a repository for genetic material from patients and their families to enable the identification of the genes involved in susceptibility to lupus erythematosus. In addition, we have established a registry for patients with neonatal lupus. The NIAMS places great significance on disseminating research information to minority groups. For example, the Institute has distributed the booklet, "What Black Women Should Know about Lupus." The NIAMS continues to work to ensure that all Americans have access to the latest research results.

CLINICAL TRIALS

Mr. Stokes: What are some of your Institute's most significant clinical trials? What can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Katz: In FY 1995, the NIAMS funded 30 clinical trials totaling \$7,660,318. This includes such studies as "Coping with Osteoarthritic Knee Pain," "Effect of Race on Bone Density in Children," "Oral Contraceptives and Hormonal Replacement in Systemic Lupus Erythematosus," "Novel Treatments for HIV-1 Related Psoriasis," and "Treatment of HIV/AIDS-Related Skin Diseases." Although none of the trials were completed during FY 1995, some interesting findings have nonetheless become apparent. For example, one of the major goals of osteoporosis research is to identify people at a high risk for fracture before a fracture actually occurs. NIAMS supported research has revealed that quantitative ultrasound--a technique for measuring bone mineral density--offers a faster, cheaper, and radiation-free alternative to other measures of bone mineral density for the assessment of osteoporosis. The ability of ultrasound measurements to discriminate those at higher risk of fracture will facilitate the targeting of individuals for preventive therapy.

We expect to report additional findings from all of these trials over the next few years -- trials that span the research areas of the Institute and cover many of the diseases that compromise life for the American public.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Katz: The FY 1997 budget request includes \$9.45 million for clinical trials. This amount reflects an increase of \$180,000 or 1.9 percent over the FY 1996 estimate of \$9.27 million; an increase of \$718,000 or 8.0% over FY 1995; and an increase of \$3.693 million or 64.1% over FY 1994.

Mr. Stokes: What is the Institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Katz: The NIH published new "NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research" in the Federal Register on March 28, 1994, and the NIH Guide for Grants and Contracts on March 18, 1994. Among the provisions in these guidelines are special requirements for clinical research trials and requirements for additional tracking of compliance from the time applications or proposals are submitted until grants and contracts are terminated. The NIAMS remains committed to ensuring that clinical research we support is inclusive of women and minorities.

PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997 budget for the Institute's outreach and public administration programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Katz: The dissemination of research results to patients and their families as well as to health care providers is vitally important. If new understandings of the causes, diagnosis, treatment and prevention of diseases are not widely shared, their value is greatly diminished. The NIAMS takes very seriously our mandate to share research findings in timely and comprehensive ways. Selected examples of this dissemination include:

- (1) The NIAMS is supporting a consortium of the National Osteoporosis Foundation, the Paget's Foundation, and the Osteogenesis Imperfecta Foundation to develop a Resource Center for bone diseases. The Center's purpose is to (a) expand awareness and enhance knowledge and understanding of the prevention, early detection, and treatment of osteoporosis and related bone diseases; and (b) broaden the knowledge base to enhance primary prevention of osteoporosis and reduce its consequences among at-risk population. The Center is addressing postmenopausal osteoporosis; osteoporosis in men; osteoporosis in high-risk populations; osteoporosis in hard-to-reach populations, including minority, low income, rural, or non-English speaking populations; corticosteroid-induced osteoporosis; and similar projects for Paget's disease, osteogenesis imperfecta, and other bone diseases.
- (2) The NIAMS develops and widely distributes news releases describing NIAMS-supported research to print and broadcast media as well as to voluntary and professional organizations that more directly reach patients and physicians;
- (3) The National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse has identified over 50 topics that are our most common inquiry subjects among the hundreds of topics that we cover. We provide regularly updated information on these subjects, including information sources, question-and-answer fact sheets, glossaries, and lay and technical articles.
- (4) We know that young black women are at high risk of lupus and its more severe complications. In our continuing efforts to alert young black women to the symptoms of lupus, we have focused on community organizations that serve these women instead of conducting the usual mass media campaign. We identified 12 cities with significant black populations and developed extensive mailing lists to provide program planning kits to some 6,500 organizations in these cities. The community organizations have requested 2,600 additional materials on lupus to distribute to their constituents. and
- (5) Access to information has been expanded by the installation of a toll free number and a TTY telephone for persons with hearing or communication impairments. Patient information is also available in large print and in Spanish. Public education information has been posted on home pages on the internet for osteoporosis and for osteogenesis imperfecta and the NIAMS has recently established its own home page.

These examples are a sampling of the many strategies the NIAMS employs to ensure information is disseminated widely and in a timely way.

The FY 1997 budget request includes \$1.7 million for public education. This amount reflects an increase of \$100,000 or 6.3% over the FY 1996 estimate of \$1.6 million; an increase of \$135,000 or 8.6% over the FY 1995 actual of \$1.565 million; and an increase of \$244,000 or 16.8% over the FY 1994 actual of \$1.456 million.

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account. Is this the case in your Institute? If yes, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Katz: The NIAMS funds approximately 30 percent of its public information activities from the research management and support mechanism. The National Arthritis and Musculoskeletal and Skin Diseases Clearinghouse and the Osteoporosis and Related Bone Diseases National Resource Center are funded extramurally. Despite the cuts to the research management and support mechanism, the Institute has been able to adequately maintain its public education efforts.

OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: What collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the Office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Katz: The NIAMS is engaged in a number of very effective collaborations with the NIH Office of Research on Minority Health. Examples of these collaborative efforts include, the clinical study "Safety of Estrogens for Women with Lupus" to study the effects of estrogens on lupus disease activity, the Minority Investigators Workshop that assembled young investigators supported through the Minority Investigator Supplement Program for career development purposes (held at the NIH on April 16, 1996), and supplements to grant awards. In addition to these formal collaborations, the NIAMS and the Office of Research on Minority Health enjoy a very close collegial relationship that greatly enhances the many research areas we share in common. There are no NIAMS awards totally funded with resources from the Office of Research on Minority Health.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the Office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Katz: The NIH Office of Research on Minority Health (ORMH), supports activities in two key areas: (1) research on health problems that disproportionately affect minority Americans, and (2) research training and education programs aimed at increasing the number of biomedical scientists who are members of underrepresented minority populations. The NIAMS projects selected for co-funding by the ORMH help to fulfill this goal.

Listed below are the projects which are co-funded between NIAMS and the ORMH. Please note, the period of performance indicates the entire project period. The dollars reflected in the amount column reflect only the dollars obligated during the fiscal year indicated.

Co-funding dollars received from the ORMH are negotiated separately each fiscal year.

FY 1995 Funding

<u>Title</u>	<u>Amount</u>	<u>Percentage</u>	<u>Period of Performance</u>
Safety of Estrogen in Lupus Erythematosus National Assessment Trial			
ORMH	\$450,000	35	
NIAMS	390,000	30	
Other	<u>450,000</u>	35	
Total	\$1,290,000		9/30/95 - 9/29/99
Peptide Induced Lupus Autoimmunity Research (Research grant supplement)			
ORMH	\$48,130		
NIAMS	Parent Grant		9/30/95 - 8/1/96

FY 1996 Estimate

<u>Title</u>	<u>Amount</u>	<u>Percentage</u>	<u>Period of Performance</u>
Safety of Estrogen in Lupus Erythematosus National Assessment Trial			
ORMH	\$450,000	35	
NIAMS	650,000	50	
Other	<u>200,000</u>	15	
Total	\$1,300,000		9/30/95 - 9/29/99
Workshop: Enhancing Career Development			
ORMH	\$50,000	67	
NIAMS	<u>25,000</u>	33	
Total	\$75,000		Apr 15 - 16, 1996
Fc Receptor Function in Normals and SLE (Research Grant Supplement)			
ORMH	\$50,000		
NIAMS	Parent Grant		9/01/95 - 8/31/97
Gene Mapping in Women with Systemic Lupus Erythematosus			
ORMH	\$200,000	26	
NIAMS	<u>565,000</u>	74	
Total	\$765,000		12/01/95 - 11/30/00

NATIONAL INSTITUTE ON AGING
RESEARCH CENTERS

Mr. Porter: Identify the number, types and subject matter of research centers funded in 1995, including the Alzheimer's Disease satellite centers.

Dr. Hodes: In FY 1995, the NIA supported 63 centers. Included are 27 Alzheimer's Disease (AD) Centers, 10 Older Americans' Independence Centers (Pepper Centers), 6 Applied Gerontology Centers, 9 Demographic Centers on Population Aging, 3 Rural Health Centers, 3 Nathan Shock Centers of Excellence in the Biology of Aging, 2 Exploratory Centers for Research on Health Promotion in Older Minority Populations, 2 Breast Cancer Centers, and 1 Core Center. In addition, the NIA has 26 Alzheimer's disease satellite clinics that complement the Alzheimer's Disease Centers.

The Alzheimer's Disease Centers support a full range of Alzheimer's disease research. These centers support shared resources and facilities for research on AD, allowing a number of investigators, many of whom are supported directly by the center grants, to provide a multidisciplinary approach to a joint research effort; or, for researchers from the same discipline to focus on a common research problem. The centers also offer ancillary supportive activities such as following patients over long periods. Additionally, centers serve as regional resources for special research purposes, such as information dissemination targeted towards health practitioners and other outreach activities. The Alzheimer's disease satellite clinics complement the AD Centers by serving as vehicles to target minority, rural or other underserved populations and enhance the clinical research capabilities of the AD centers through the diversification of the research patient pool.

The Older Americans' Independence Centers were authorized by Congress to conduct research to develop and test interventions to help older people continue to live independently and avoid institutionalization or prolonged hospitalization. These centers focus on topics such as prevention of falls, strength and balance training, and prevention and treatment of incontinence. The Applied Gerontology Centers feature studies of social and behavioral interventions to prevent dependenc, such as driving ability and prevention of crashes, caregiving, and computer skills.

The Demographic Centers on Population Aging apply state-of-the-art demographic, economic and mathematical methods to new databases and assist in the continuation of demographic research utilizing data gained from studies such as the Health and Retirement Survey. The Rural Health Centers focus on the changing sociodemographic and epidemiologic characteristics of the older rural population. The Exploratory Centers for Research on Health Promotion in Older Minority Populations study health status, health behavior and practices, and interventions for improving the health of older Black, Hispanic, and Asian Americans.

In FY 1995, the Nathan Shock Centers of Excellence in the Biology of Aging were established to enhance the quality of research in the basic biology of aging, and facilitate the planning and coordination of aging research activities. The Breast Cancer Centers grants were awarded to develop a broad array of basic, clinical and prevention and control research to reduce the incidence and mortality of breast cancer on a local, regional, and/or national level. The Core Center provides support for the operation of key epidemiological and demographic studies.

TARGETS FOR INTERVENTION

Mr. Stokes: As you are aware, hypertension, cardiovascular disease and stroke continue to take a major death and disability toll on older Americans and a disproportionate toll on older African-Americans. Are there any new findings from NIA-supported research that present potential targets for intervention?

Dr. Hodes: It is known that the frequency of high blood pressure (hypertension) in African Americans is one of the highest in the world and that, at any decade of life, high blood pressure is more severe in African Americans than in Whites. Also, the prevalence of high blood pressure in elderly African Americans, age 60 and older, is approximately seventy-one percent. This higher prevalence places elderly African Americans at greater risk for fatal and non-fatal stroke, heart disease and heart disease-related deaths, and end-stage renal disease.

To address this minority health concern, NIA recently published a program announcement on "Aging, Vascular Stiffness, and Cardiovascular Function." The purpose is to foster extramural biomedical research which will augment our understanding of blood vessel stiffening during aging. Once thought to be a part of normal aging without adverse consequences, stiffening of the large elastic arteries (e.g., the aorta) during aging may lead to a special type of hypertension, isolated systolic hypertension, and increased susceptibility to cardiovascular disease including heart disease and stroke. The importance of blood vessel stiffening during aging in contributing to hypertension and development of cardiovascular disease in African Americans is currently unknown. One emphasis of the program announcement is to address blood vessel stiffening in minority populations, including African Americans. NIA is now beginning to receive applications in response to this announcement.

NIA intramural scientists have recently shown that the expected age-associated increase in blood vessel stiffening is reduced in older persons who have a history of exercise conditioning. Present research is exploring the ability of exercise and drug medications to reduce blood vessel stiffening in older adults, especially those persons with high blood pressure and heart failure. NIA scientists are conducting part of this research in collaboration with their NHLBI colleagues.

Understanding the importance of blood vessel stiffening in aging, and in cardiovascular disease, may lead to development of preventive strategies (e.g., modification of risk factors through exercise and/or diet interventions) or new therapeutic strategies (e.g., novel drug development or even gene therapy) to prevent, delay, arrest, or even reverse blood vessel stiffening and its potential harmful effects.

MINORITY RESEARCH INVESTIGATORS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under its purview?

Dr. Hodes: The National Institute on Aging has a variety of programs in place to improve the diversity profile of the total number of investigators engaged in aging research. NIA regularly participates in the NIH-wide minority supplement program to support African American and other minority investigators conducting aging research. Some of these supplements go to MERIT awardees, recognized leaders in aging research, to recruit minority students or investigators. The minority investigators being supported range from fully trained investigators to postdoctoral, graduate, and undergraduate students.

The NIA further acts to increase the number of minority investigators by providing an additional training slot for a minority predoctoral or postdoctoral student on training grants supported by the Institute. This creates opportunities for advanced minority students to become fully trained investigators. NIA also makes dissertation research awards to minority students enabling them to complete research required for their doctoral degrees.

During the past year, the Centers for Minority Aging and Health Promotion have successfully engaged in three related activities to enhance research on minority aging. These include: 1) increasing collaboration between minority and majority institutions; 2) increasing the competitiveness of minority researchers; and 3) advancing methodologies for recruiting minority subjects. These Centers have played an increasingly important role in training minority researchers at every level from college to senior investigators. These Centers have provided training/research experience for almost 50 minority researchers.

With input from staff minority scientists, NIA will continue to develop strategies to attract minority investigators and postdoctoral fellows to NIA. All scientists are encouraged to recruit minorities for positions when attending conferences and visiting academic institutions. In addition, a recruitment incentive award has been developed to promote proactive recruitment efforts aimed at improving workforce diversity, including postdoctoral fellows and investigators.

Mr. Stokes: What efforts has your Institute undertaken to educate minorities on opportunities that are available in biomedical research?

Dr. Hodes: In addition to the programs mentioned above that involve minority students and scientists in biomedical and behavioral research directly, the NIA, through its Minority Working Group, conducts at least two regional outreach technical assistance workshops each year to educate minorities about opportunities in aging research and to assist minorities in preparation of their research and training applications. NIA maintains a listing of all participants, many of whom are minorities, in the NIA sponsored regional meetings, and provides them information on biomedical research opportunities at NIA and NIH. These participants are from majority and minority academic institutions and other biomedical organizations, and these meetings are held in areas that have institutions with high minority enrollments. The NIA Minority Working Group also publishes a newsletter containing information about research opportunities for interested minority scientists and students, and other researchers.

NIA conducts a Summer Institute on Aging Research that is attended by a substantial proportion of minority persons who are interested in research on aging. Information about the Summer Institute is disseminated in journals and newsletters designed to reach a large audience; its agenda has always included minority health and aging as a substantive area.

The NIA supports the participation of staff at biomedical conferences with a large percentage of minority students and faculty. In the NIA laboratories, supervisors of predoctoral and other students provide guidance on career opportunities and advice on obtaining financial support for their graduate education in biomedical fields. I am also pleased to report that this past fall, NIA adopted an elementary school with predominantly minority enrollment. NIA scientists' interactions with students at the school have already had an impact on these young students' interest in the biomedical sciences. Recently 51 students, who were selected by the school's faculty, spent a full day at NIA laboratories visiting with investigators.

ALZHEIMER'S DISEASE RESEARCH

Mr. Stokes: There have been a remarkable sequence of findings on Alzheimer's disease. What hope do they offer for improving the care of Alzheimer's patients?

Dr. Hodes: Alzheimer's disease clearly is associated with several risk factors; foremost among these are age and genetic inheritance. The majority of early-onset cases of Alzheimer's disease are inherited. Recently, mutations have been identified in several genes that are found in families with early-onset Alzheimer's disease including the presenilin genes on chromosomes 14 and 1 and the amyloid precursor protein (APP) gene on chromosome 21. The inheritance of the apolipoprotein E4 gene on chromosome 19 is a risk factor for late-onset sporadic Alzheimer's disease, and the association of apolipoprotein E4 with altered performance of short term memory tasks has been confirmed in subjects studied by NIA's intramural scientists.

Research findings such as these will lead the way toward developing new strategies for the diagnosis of Alzheimer's disease as well as providing targets for the development of new drugs to treat Alzheimer's disease. This genetic research, along with advances in understanding of mechanisms in the brain, such as beta-amyloid peptides and oxygen free radicals, which result in dysfunction and death of nerve cells, will lead ultimately to therapeutic interventions which will improve the management and care of patients with Alzheimer's disease.

Early diagnosis is an important component of reducing the morbidity associated with Alzheimer's disease since it seems likely that any therapeutic intervention will have greater success in less severe cases. One promising approach to early diagnosis is the use of functional positron emission tomography (PET) imaging since there is evidence that alterations in the PET scan precede the development of impaired performance on memory tests.

Currently, NIA supports two multi-center collaborative efforts focused directly on examining care for persons with dementia. REACH (Resources for Enhancing Alzheimer's Caregiver Health) is a new six site study to examine the stresses experienced by caregivers. Results are just beginning to emerge from a second collaborative study examining institutional dementia specialized care units and their impact on nursing home residents, family, and nursing home staff. These units appear to have positive benefits on care practices (e.g., fewer restraints used); are viewed positively by families as helping their loved ones; and reduce some stress on the caregiving staff.

Mr. Stokes: How does NIA coordinate its Alzheimer's disease research efforts with those of other NIH Institutes?

Dr. Hodes: The National Institute on Aging, in conjunction with the National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health, and the National Institute of Nursing Research has initiated the Inter-Institute Alzheimer's Disease Working Group. This Group includes the Director and relevant program staff of each of the four institutes. Participants meet at least quarterly to discuss new scientific opportunities and currently supported research and to coordinate grant funding and other matters of common interest regarding Alzheimer's disease. For example, the last meeting included discussion of the research being supported by the institutes in the area of Alzheimer's disease genetics, which has been generating a great deal of excitement with the discovery last year of two genes for early onset familial Alzheimer's disease. It is expected that these meetings will generate opportunities for joint program announcements and funding of Alzheimer's disease research, such as in the area of the structural biology of proteins associated with Alzheimer's disease which is of common interest among the institutes.

Mr. Stokes: What is the cost of Alzheimer's disease to the nation? What is the total amount of funds invested in Alzheimer's disease research by the NIH?

Dr. Hodes: It is estimated that there are up to four million Americans currently suffering from Alzheimer's disease and, due to the projected growth of the older population, perhaps as many as 15 to 20 million will experience the devastating effects of this disease in the early 21st century. The staggering economic burden of Alzheimer's disease to families and society is currently estimated to be as high as \$100 billion per year. In FY 1995, the NIH funding for Alzheimer's disease research was \$296,741,000 with NIA representing approximately 72 percent, or \$214,962,000, of the total investment. FY 1996 and FY 1997 estimates for Alzheimer's disease research across NIH are \$308,717,000 and \$314,159,000 respectively.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum. What are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997

budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Hodes: The NIA has an active outreach and public education program, the most visible of which is the Alzheimer's Disease Education and Referral (ADEAR) Center. The ADEAR Center serves as a national resource for accurate and timely information about Alzheimer's disease (AD), its consequences and potential treatment, research results, and AD services available to the public, patients and their families, and health professionals.

Information specialists answer written and telephone requests which are most often about the disease in general, diagnosis and treatment, participation in clinical trials, research, long-term care, and caregiving. In addition to distributing hundreds of thousands of publications in response to these inquiries, specialists create packaged topical searches, which are sent primarily to professionals--physicians, activity professionals, administrators, professional caregivers, social service providers, and Congressional staff. To date, more than 20,000 searches have been distributed.

Publications written and produced include research reports, fact sheets, bibliographies, and resource directories. This material makes scientific information and research results more accessible to a variety of public and professional audiences. The quarterly newsletter, *Connections*, is written and distributed to more than 11,000 professionals and other interested members of the public. This award-winning newsletter serves as a link between the Institute, NIA-supported research centers, and the private sector.

In a special effort to educate physicians in addressing the special needs of their older patients, the NIA has produced information on how to optimize doctor/patient communications. To encourage physicians to utilize this information, the Institute has secured continuing medical education credits for the activity. Simultaneously, the NIA launched a television-based public education campaign for older people encouraging them to call for a free booklet on how to talk to their doctor more effectively. The Institute is now planning an education campaign and preparing written materials to educate older people to the importance of physical fitness, especially strength training, in maintaining their health and independence.

The NIA also fosters outreach/education activities through its extramural program, one of the most significant of which is part of NIA's Alzheimer's Disease Center program, and is known as the Satellite Diagnostic and Treatment Clinics program. The Satellite clinics are designed to educate minority and other underserved communities about AD and to offer participation in research protocols. This facilitates diversification of the patient pool as well as providing very basic support services to underserved communities.

Estimated funding for the ADEAR center and the outreach and education activities associated with the Alzheimer's centers and their satellites totals \$4.9

million per year for both FY 1997 and FY 1996. This compares with an annual level of \$5.0 million for FY 1995 and \$5.5 million for FY 1994.

Several other centers within NIA's extramural program include outreach and education activities as part of their functions. The Older Americans' Independence Centers include an information dissemination component to translate findings from their research to develop better clinical treatments and preventive approaches. The Applied Gerontology Research Centers are designed to move promising social and behavioral research findings, such as computer skills, driving, exercise, caregiving, and nursing home care, out of the laboratory and into programs that can help improve the lives of older people and their families. Several of the Centers for Research on Health Promotion in Older Minority Populations have an active research dissemination core. This is especially important in order to enhance the recruitment and retention of minority subjects.

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account. Is this the case in your Institute? If yes, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Hodes: Some of the NIA's outreach/educational programs are supported through extramural mechanisms, such as the satellite clinics supported by the Alzheimer's Disease Centers. The ADEAR Center is funded by the Research Management and Support (RMS) mechanism. The mandated reductions in RMS for FY 1996 have necessitated a decreased level of funding for all RMS activities.

BASIC RESEARCH ON AGING

Mr. Stokes: The NIH supports a strong program of basic research with promise for improved prevention and treatment of disease. What does the Institute do to ensure that advances from basic research are translated into interventions that help to improve the quality of life for seniors?

Dr. Hodes: Since NIA's goals are to prevent disease and disability and to improve treatments, the Institute employs several means to ensure that scientific findings are translated expeditiously from the laboratory into practical applications. For example, transfer of basic research findings to clinical practice is at the core of NIA's centers programs. Our Older Americans Independence Centers have developed and tested successful new strategies to prevent disability based on findings that targeted risk factors for falls and hip fractures. The first randomized controlled trial using this multiple risk factor approach reduced falls by nearly half and also saved substantial health care costs. Our Alzheimer's Disease Centers foster collaboration between basic and clinical researchers to capitalize on promising leads, and four compounds are now in trials to test their clinical safety and efficacy. In addition, NIA established the innovative NIA Drug Discovery Groups to speed the discovery, development, and testing of new compounds and delivery systems for treatment of Alzheimer's disease. Our Exploratory Centers for Health Promotion in Older Minority Populations foster development of improved self-care and preventive practices in older African-American, Hispanic,

and other minority populations through the translation of research findings into health promotion interventions. NIA's Roybal Centers in Applied Gerontology translate behavioral and social research findings into practical outcomes that maintain health and prevent or overcome disability.

In addition, a special translation initiative begun this year involves all NIA programs in identifying scientific findings with special promise for maintaining health and quality of life in old age, such as hormone replacement and nutritional supplements. Through this initiative, NIA will work to ensure that the findings are properly tested in older people and widely disseminated to the public and health care practitioners.

CLINICAL TRIALS

Mr. Stokes: What are some of your Institute's most significant clinical trials? What can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Hodes: I am pleased to describe for you several of NIA's most significant clinical trials and the results of those trials for which data has been analyzed and published. NIA's Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) initiative supported research to improve physical functioning in old age. Research from FICSIT trials has demonstrated the benefits of strength training for older people and the value and cost-effectiveness of targeted, fall prevention programs for the elderly. It is estimated that each year falls are responsible for costs of over \$12 billion in the U.S., and the costs due to physical frailty are much higher. Two studies within this initiative are the first involving Tai Chi to be reported by scientists in a special frailty reduction program. Tai Chi is a martial arts form that enhances balance and body awareness through slow, graceful, and precise body movements. In the first study, investigators found that older people taking part in a 15-week Tai Chi program reduced their risk of falling by 47.5 percent. A second study found that several interventions to improve balance and strength among older people were effective. These improvements, particularly in strength, were preserved over a 6-month period while participants did Tai Chi exercises. The news comes in two reports appearing in the May 1996 *Journal of the American Geriatrics Society*. It is a strong reminder that relatively "low tech" approaches should not be overlooked in the search for ways to prevent disability and maintain physical performance in late life.

A new system of hospital care, developed by the NIA supported Older Americans' Independence Center in Cleveland, called the Acute Care for Elders (ACE), is helping older people to maintain their functional independence during hospitalization, thereby lessening their need for long-term care after discharge. When older people are hospitalized, they often lose their ability to take care of themselves, despite appropriate treatment of their disease. ACE encourages patients to maintain or achieve independence in important activities of everyday life, such as bathing, dressing, and moving about a room. Two major findings have resulted from the ACE study. First, loss of independence is not an inevitable consequence of acute illness and hospitalization for elders. Second, the ACE unit

provides a model for improving patient outcomes, such as ability to care for oneself, that are not related specifically to a single disease or treatment. Most previous efforts to improve the quality of hospital care have focused on patients with a single disease or receiving a single treatment. ACE may complement these conventional efforts, especially for older people who often have several illnesses and receive many therapies.

Sites Testing Osteoporosis Prevention/Intervention Treatments (STOP/IT) is a multicenter trial, now in its fourth year of data collection, promoting effective strategies to combat the loss of bone strength in the hips of persons age 65 and older. The sites are testing: specific weight-loading exercises for the hip; supplemental vitamin D and calcium; testosterone replacement in men; and, the use of an active form of vitamin D alone and in combination with ovarian hormones such as estrogen. In addition, investigators at the sites are studying indicators of bone strength, biochemical markers of bone and bone turnover, calcium absorption, and other topics related to osteoporosis prevention. It is expected that the findings of these studies will be published sometime during FY 1998.

The Alzheimer's Disease Cooperative Study is composed of 35 research sites and was established to conduct clinical studies of promising drugs. A study to assess the effectiveness of Deprenyl and vitamin E in slowing the course of Alzheimer's disease (AD) began in October 1992; results from this trial should be available later this year. Another study on drug and behavioral treatment of agitation began in June 1994 and is scheduled to end October 1996. A study of the anti-inflammatory drug prednisone to treat AD began in January 1995 and is scheduled to end in January 1997. The newest trial, a pilot study investigating whether or not estrogen can improve function in women with AD who had previously undergone complete hysterectomy (with removal of both ovaries), was initiated in September of 1995. Previous reports suggested that post-menopausal women on estrogen therapy experienced benefits including improvements in mood, concentration, and memory. The major question addressed by this study is whether or not women with AD who had undergone prior complete hysterectomy show benefit from a twelve-month period of estrogen therapy. Study results should be available by the end of 1997.

REACH (Resources for Enhancing Alzheimer's Caregiver Health) is a new study to examine the stresses experienced by caregivers and to test the effectiveness of different strategies for enhancing caregiver's abilities to maintain appropriate care over the course of the disease. During the first year of the study, investigators are nearing completion of a common core assessment tool to evaluate the treatment outcomes on a diverse population of caregivers (oversampled to include African Americans and Hispanic caregivers). Pilot testing is also underway to refine the different intervention approaches which include behavioral skills training, individual and family systems counseling, telephone and computer assisted support networks, and environmental modifications.

A new multisite cooperative trial, Cognitive Interventions to Improve Independence, will investigate whether a cognitive or perceptual intervention can maintain and promote independent functioning among older adults who are at

increased risk of loss of independence through hospitalization, need for formal care, or other major restriction in quality of life. The intervention will be tested with different samples of subjects, varying in racial, ethnic, gender, socioeconomic, and cognitive characteristics. Awards are planned for September, 1996.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Hodes: The FY 1996 and FY 1997 estimates for funding of clinical trials are \$15,587,000 and \$15,292,000 respectively. In FY 1994 the amount of funding for clinical trials was \$13,062,000 and in FY 1995, the amount was \$12,811,000.

Mr. Stokes: What is the Institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Hodes: The NIA follows NIH policy that women and members of minority groups must be appropriately included in clinical research, including clinical trials, unless there is a compelling rationale not to include them. Cost is not an acceptable reason for exclusion. Specific to clinical trials, where strong evidence that differences by gender or by ethnic status exist, the study must be designed with adequate statistical power to provide tests of the intervention in the separate groups. For clinical trials in which there is insufficient evidence that differences by gender or ethnic status exist, the study must be designed to allow a valid analysis by subgroup.

CELLULAR AND MOLECULAR RESEARCH

Mr. Stokes: With respect to the health of older Americans, what is the importance of the Institute's research on cellular and molecular changes with age?

Dr. Hodes: Human aging is accompanied by various degrees of functional decline in the tissues and organ systems of the body. Some examples where functional decline is known to significantly impact the health and quality of life of older Americans include the musculoskeletal (muscle, bone, cartilage), cardiovascular, nervous, and immune systems. Understanding the cellular, biochemical and molecular changes which occur in these and other systems with age, and the underlying basic mechanisms responsible for these changes, are important steps in the development of rational interventions and therapies to prevent and/or delay the onset of age-related changes in body function and the appearance of age-related diseases. The investment in NIA-funded research to understand the cellular, biochemical and molecular mechanisms of aging holds the promise of increasing the healthspan (portion of life in which we are healthy and functionally independent), improving the quality of life, and decreasing the health care costs of older Americans now and in the future.

For example, detrimental age-related changes in the musculoskeletal system include loss of skeletal muscle mass, strength and functional capability. Bone mass, strength and quality are also significantly decreased with advancing age. In

addition, degenerative changes in connective tissues (cartilage, tendons) are also prevalent. Studies to understand the biological bases of these age-related changes in the tissues of the musculoskeletal system have revealed that the properties of specialized cells in muscle, bone and cartilage are altered in older individuals. Age-related changes in the production of key biological regulatory molecules, cellular responses to these biological signals, and ultimately alterations in gene expression and its regulation have been uncovered recently. Further research focused on defining the biological mechanisms underlying these changes will provide the necessary scientific basis for the design of interventions to prevent or retard the onset of musculoskeletal decline.

To cite another area of current interest, both the NIA intramural and extramural research programs support basic research to understand the contributions and consequences of oxidative damage to cellular macromolecules (DNA, RNA proteins, membrane lipids) in normal aging and the development of age-related diseases. Oxidative damage results from normal oxygen-dependent metabolism within the cells and unrepaired damage has been shown to accumulate with aging. NIA places high priority on cellular and molecular research to unravel the biological consequences of oxidative damage, to define the mechanisms involved in cellular repair processes, and to identify and test dietary or other agents which may prevent age-related accumulation of DNA damage. It is believed that the information gained from such work will enable us to develop interventions to extend human healthspan and prevent the occurrence of age-related diseases like heart disease and cancer which cause the majority of human morbidity and mortality in the elderly American population.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: For the activities that are under the purview of your Institute, where are we now with respect to closing the gap in minority health? Specifically, what progress do you have to report to the subcommittee this year?

Dr. Hodes: Older Americans, even the oldest, can expect to live years longer than those who reached the same ages even a few decades ago. Though survival has improved for all racial and ethnic groups, the gap between minorities and non-minorities has not closed, neither in life expectancy nor in levels of disability and death at older ages. Published death rates for those over age 80 have historically been lower for African Americans than for Whites. However, recent research by NIA grantees suggests that the observed "crossover" at older ages is not real, but results from errors in the age at death data for African Americans at the oldest ages. After adjusting for this age misreporting, previously reported life expectancy at older ages for African Americans could in fact be as much as two years too high, making the gap in minority health even wider. Several NIA initiatives are designed to develop much needed information on the characteristics of the gap so that it will be known into which areas resources should be placed.

An NIA-funded epidemiologic study based at Duke University is looking at a variety of mental, physical and dental health problems among African Americans and Whites, ages 65 and older, who live in rural and urban areas of the North

Carolina Piedmont. Cognitive and psychosocial functioning are of particular interest as is the interplay of socioeconomic and health characteristics of this population.

Both the Health and Retirement Study (HRS) and the Survey of Asset and Health Dynamics Among the Oldest Old (AHEAD), nationally representative NIA-funded surveys of the economic and health security of America's population age 51 and over, contain large oversamples of African Americans and Hispanics. Once these surveys reach their longitudinal potential, they will help us untangle the relationships among health, income, wealth and family structure for African Americans and Hispanics. Preliminary findings have shown large differences between African Americans and Whites in self-reported health, income and wealth, with differences in education, income and family net worth accounting for much of the gap in health.

In collaboration with the Office for Research on Minority Health, NIH, the NIA established six Centers for Research on Health Promotion in Older Minority Populations. The purpose of these Centers is to increase research on minority health status, health practices, and interventions for improving the health of older African Americans, Hispanic, and Asian Americans. Investigators are designing culturally sensitive interventions to promote exercise and appropriate dietary behaviors, as well as to increase older people's recognition and responses to symptoms related to chronic diseases. These Centers have been especially successful in serving as a resource to further minority aging research and the training of minority researchers.

Other ongoing NIA-funded studies are examining the determinants of physical frailty in minorities to find out if there are ethnic differences in the factors contributing to frailty. These studies are nearing completion and if there are ethnic differences, it is anticipated that data from these studies will substantially guide the development of effective interventions for physical frailty in minority populations.

It is known that the frequency of high blood pressure (i.e., hypertension) in African Americans is the highest in the world and that, at any decade of life, high blood pressure is more severe in African Americans than in Whites. This higher prevalence places elderly African Americans at greater risk of cardiovascular disease-related morbidity, disability and premature mortality. In response to this health issue, NIA recently published a program announcement to foster research on blood vessel stiffening and hypertension during aging, especially among minority populations.

DISABILITY IN THE OLDER POPULATION

Mr. Stokes: Disability in older people results in a large proportion of Federal health care costs through Medicare and Medicaid. I have read about the research NIA funded that helped people in their nineties and older, increase their strength and mobility through programs of weight lifting and exercise. What new scientific opportunities is NIA pursuing to prevent disability in older people?

Dr. Hodes: NIA supports and conducts research on various aspects of physical disability, which range from small-scale clinical studies of exercise and nutritional and hormonal interventions to population-based epidemiological studies which document the progression of disability in the elderly. An area of emerging interest in research on disabilities is the development of "targeted" interventions. For example, physical functional independence is related to multiple factors, including an individual's muscle strength, flexibility, coordination and endurance. Functional impairments and disability may result from a deficit in one or a combination of these factors. For instance, the ability to carry a bag of groceries home is an activity of everyday life. This common task may be difficult for some elderly individuals to perform because they may lack the muscle strength to pick the bag of groceries up, or they may lack the endurance to carry the bag a certain distance and/or they may not be able to avoid tripping or falls due to mobility, balance or vision problems. Therefore, an intervention "targeted" to improve specific deficits in performance may provide greater benefits in functional outcome than a generalized exercise program.

The example of the ability to carry a bag of groceries also underscores the importance of determining the underlying mechanisms of functional decline and disability so that targeted interventions can be developed. A number of age associated changes and diseases, including age associated losses of strength, muscle mass (sarcopenia), motor control, bone density (osteoporosis), and diseases including those of the joints (osteoarthritis), and cardiovascular system (heart failure and stroke), as well as environmental factors (falls), play critical roles in the onset of disability in old age. The NIA conducts and supports an active research portfolio in these areas which typify research on disability and in the behavioral aspects of disability in the elderly.

Progressive loss of muscle mass, or sarcopenia, has been hypothesized to be a common pathway by which multiple diseases contribute to disability. However, there are critical gaps in our knowledge on the epidemiology of this condition; an incomplete assessment of the clinical significance of the age-related changes in skeletal muscle mass, strength and quality; and a poor understanding of the underlying mechanisms responsible for the age-related decline in skeletal muscle mass and function. It is anticipated that collaborative activities between the NIA and the research community will stimulate studies focusing on these important aspects of the relationship between age-related changes in skeletal muscle and the development of disability.

The NIA is initiating a new clinical research study, the Dynamics of Health, Aging and Body Composition (HEALTH ABC), to characterize the extent of loss of muscle mass in older men and women, identify clinical conditions accelerating the loss of muscle, and examine the health impact of loss of muscle on strength, endurance, disability and diseases common in old age. Approximately 3,000 older men and women, half of whom will be African-American, will be enrolled at two clinical centers and followed for 7 years for new onset of physical disability. This study will provide invaluable information on optimal timing for interventions to prevent or reverse muscle loss and on high risk groups most likely to benefit.

Each year, thousands of older Americans, more women than men, are admitted to costly long-term care facilities due to hip fracture, for which osteoporosis is a major risk factor. NIA-supported osteoporosis research includes clinical studies of age-related bone loss and fracture epidemiology, intervention trials to prevent or reverse bone loss, and basic laboratory studies on the biology of osteoporosis and bone cell function. Results of studies are encouraging as to the potential for preventing bone loss and related fractures. Intramural researchers are investigating several interventions for treatment of osteoporosis, including enzyme regulation, cell replacement, and growth factor supplementation. These scientists have found that anticollagenase (an enzyme) treatment can prevent the bone loss seen in certain laboratory animals used to study osteoporosis. It is hoped that these studies will lead to the development of interventions for trial in patients to determine if such an approach will work as a treatment for osteoporosis in humans.

Cartilage is the specialized cushioning tissue in joints that undergoes age associated changes which subsequently lead to osteoarthritis (OA). Researchers are involved in studies directed toward: 1) identifying regulatory mechanisms for cartilage-specific genes, 2) establishing the potential for cell based cartilage repair, and 3) determining the role of cell death in cartilage degeneration. Other NIA-funded research in this area has been focusing on the development of new exercise interventions to strengthen the joints affected by OA and of new drug treatments of OA. Intramural research has led to the development and evaluation of new scales for evaluating individual features of OA in radiographs. Using these scales, researchers have evaluated the incidence, prevalence and progression of osteoarthritis in healthy individuals as they age.

Falls are a frequent cause of disability in the elderly because of the high incidence of hip fracture. The cause of falls is multifactorial, including weakness, sensory loss and poor balance. Both extramural and intramural scientists are examining factors that contribute to falls, factors that affect hospital outcome in hip fracture patients, and strategies for prevention of falls in nursing home settings. The goal of this field is to develop safer and friendlier environments for the elderly which maximize functional performance and minimize injuries.

As an example of behavioral research directed at prevention of disability, NIA funds research in the area of "Self Care in Later Life," in other words, what older people can do to maintain their health and functioning despite the presence of chronic diseases or illnesses. In addition to research on health promoting practices such as exercise, investigators are also examining how older people interpret and act upon illness symptoms in order to reduce unnecessary delays in seeking appropriate care. Other research focuses on the older patient-doctor interaction, examining how doctors can increase older people's preventive and rehabilitative health practices, and how doctors themselves can increase their own sensitivities to the identification of geriatric conditions.

HEALTH OF OLDER WOMEN

Mr. Stokes: Women make up approximately 60 percent of people age 65 and over and some 72 percent of people age 85 and over. What is the Institute doing to improve the health of older women?

Dr. Hodes: Compared to men, older women are more likely to have functional limitations and disability, to live longer with their disability, and are more likely to require institutionalization. Much of the work supported by the NIA is of direct relevance to the health concerns of older women; several key research initiatives are described as follows:

The Women's Health and Aging Study is a community-based prospective epidemiologic study whose goal is to study the causes and course of physical disability in the one-third most disabled women living in the community. A total of 1,002 women in Baltimore County and City met the criteria for the study, were enrolled, and underwent comprehensive evaluations in their homes between 1992 and 1995. Participants are presently at various stages in the follow-up process, depending on when they entered the study. The cohort will be followed for 3 years, with follow-up assessments performed every 6 months in order to identify medical events and transitions in function that may occur quite rapidly in this population. Women in the study will also be monitored for hospitalization, nursing home admission, the use of home health care, and mortality. No study has ever obtained such detailed information on the medical, psychological, and social characteristics of older women with impaired physical functioning. Data from the baseline assessments of these women are presented in a book published in November 1995, *The Women's Health and Aging Study: Health and Social Characteristics of Older Women with Disability*.

Initiated in September 1994, the Study of Women's Health Across the Nation (SWAN) is a five-year study of 3,200 women which will evaluate the effect of the menopausal transition on subsequent health and risk factors for age-related diseases common in older women and responsible for significant morbidity and mortality. Diseases of particular interest include osteoporosis, diabetes and cardiovascular disease. The study population consists of African American, Chinese, Japanese, Hispanic and Caucasian women from seven clinical sites across the nation. Five of the seven clinical sites comprising this NIA study conduct prospective longitudinal studies to determine the differential contributions of age and ovarian hormone status to changes in bone mass as women approach and traverse menopause. Some sites explore underlying mechanisms whereby menopause-related hormonal changes accelerate bone remodeling and adversely impact bone mineral metabolism.

This spring, the NIA, joined by three sister Institutes--the National Cancer Institute, the National Institute for Nursing Research, and the National Institute of Mental Health--issued a Program Announcement, Aging Women and Breast Cancer, to encourage submission of grant applications on the unique problems of older women with breast cancer. Of the 182,000 breast cancer patients diagnosed in 1994, 91,000 were women 65 years and older. The NIA is committed to

expanding the knowledge base on breast cancer in older women through studies in biology, clinical medicine, epidemiology, and the behavioral and social sciences.

Epidemiological data indicate that in women age 60 years and older, the prevalence of urinary incontinence (UI) is twice that in men. Moreover 25-30 percent of incontinent women have frequent episodes of urine leakage which may occur daily or weekly. The NIA has been supporting a number of clinical studies on behavioral (e.g., pelvic muscle exercises) and pharmacological therapies (e.g., estrogen replacement therapy) to reduce or completely cure UI in older women. These studies have demonstrated that behavioral techniques such as pelvic muscle exercises, bladder training and biofeedback are effective in the management of UI in women. The Agency for Health Care Policy Research incorporates the results from these and other studies on UI into a Clinical Practice Guideline entitled "Urinary Incontinence in Adults: Acute and Chronic Management." The most recent update of this guideline was released in March 1996. Since the management of UI is estimated to cost \$10 billion, one of the future challenges is to find ways to prevent the development of UI. An NIA-funded investigator has recently completed a pilot study on a behavioral program for the prevention of UI in women, and it is anticipated that the larger scale study will start by the end of 1996.

Osteoporosis and related bone disorders take a significant toll in old age, particularly by contributing to vertebral and hip fractures, which in turn can result in disability and mortality. The NIA supports a robust program of clinical studies of age-related bone loss and fracture epidemiology, intervention trials to prevent or reverse bone loss, and studies of the effects of sex steroids and growth factors on bone cell function. The Institute also funds basic research on bone cell biology and skeletal renewal and repair. The set of clinical trials, "Sites Testing Osteoporosis Prevention/Intervention Treatments," is now in its fourth year of data collection. This research is evaluating the effectiveness of various strategies to combat the loss of bone strength in the hips of persons age 65 and older. The investigators are studying specific weight-loading exercises for the hip, supplemental vitamin D and calcium, testosterone replacement in men, and the use of an active form of vitamin D alone and in combination with ovarian hormones such as estrogen. In addition, investigators are studying indicators of bone strength, biochemical markers of bone and bone turnover, calcium absorption, and other topics related to osteoporosis prevention.

Hip fracture is a devastating and costly injury for the elderly, and often can be marked as the event which robs many older persons of independence and productivity. The high rate of possible admissions for hip fracture (300,000 by the year 2000) and the patient's functional status at discharge from the hospital are important predictors of use of health care resources, institutionalization, and mortality. In order to facilitate recovery from hip injury, NIA intramural scientists working with the National Institute for Nursing Research, are developing behavioral nursing interventions to prevent post-operative pressure sores, urinary retention, urinary incontinence, urinary tract infection, malnourishment, and immobility.

Women are the predominant caregivers for family members as well as the predominant receivers of family care for older persons. NIA research is documenting caregiving burdens, identifying factors related to stresses and strains, and designing interventions to reduce the burdens of care. Specific initiatives have recently been instituted in two areas to increase research efforts on family structures and dynamics as related to: 1) the grandparenting role; and, 2) violence in families. These research efforts are designed to increase knowledge of factors associated with family strengths and to identify areas where families may need additional assistance in coping with caregiving and other life challenges. A specific goal of this research is to understand varied patterns of caregiving within and across different minority and ethnic groups.

OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: What collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Hodes: In FY 1993 the NIA collaborated with the Office of Research on Minority Health (ORMH), to develop a program to establish Exploratory Centers for Research on Health Promotion in Older Minority Populations. This program was initiated to study health status, health practices and interventions for improving the health of older African Americans, Hispanic and Asian Americans. Many excellent applications were received and additional support from NIA enabled the establishment of six centers. These Centers were awarded for a period of two years, with funding extensions in FY 1995, and again in FY 1996, to allow additional time for submission of renewal applications for full centers. In FY 1995 two Centers were supported totally by ORMH--the Rand Corporation Center for \$530,000 and the Harvard Center for \$585,000. Two others were supported totally by NIA--the Center at Rutgers University for \$465,000 and the University of Texas Health Science Center for \$428,000. The last two Centers were jointly funded. The total amount of FY 1995 funding received from ORMH for this effort was approximately \$2,000,000.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, include their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Hodes: As indicated above, the Exploratory Centers for Research on Health Promotion in Older Minority Populations are supported by the Institute and the ORMH. These Centers were awarded also for a period of two years, with funding extensions in FY 1995, and again in FY 1996, to allow additional time for

submission of renewal applications for full centers. In FY 1995, two of these Centers were co-funded by NIA and ORMH:

	<u>NIA</u>	<u>ORMH</u>	<u>TOTAL</u>
University of Illinois	\$ 10,000 (2%)	\$452,000 (98%)	\$462,000
Duke University	123,000 (19%)	508,000 (81%)	631,000

NATIONAL INSTITUTE OF DENTAL RESEARCH

STRATEGIC PLAN

Mr. Porter: Dr. Slavkin, you announced at your January Advisory Council meeting that you planned to ask a group of outside scientists not affiliated with the Dental Institute to evaluate the Institute's research direction. Has this group begun its work, and what sort of product do you expect it to produce?

Dr. Slavkin: The National Advisory Dental Research Council determined that a fresh analysis of NIDR support of basic, translational, patient-oriented, and demonstrational scientific research should be undertaken. The analysis could validate scientific areas in which NIDR is currently engaged, as well as identify new scientific opportunities. To accomplish this analysis, the Council established a Subcommittee for Scientific Opportunities, which met on March 4-5 at NIH. The invited participants were outstanding scientists representing diverse disciplines from basic, behavioral, and clinical sciences. Their experiences, knowledge base, and interests in new thinking provided an excellent perspective from which to envision areas of scientific opportunity for the NIDR for the next 4 to 6 years. The members of the subcommittee discussed future NIDR research opportunities, changes in and expansion of training and career development, the research resources required to support new scientific opportunities, and the partnerships and collaborations that could be made with academia and industry, increasingly across a broad range of disciplines.

Mr. Porter: How will their work relate to the Institute's strategic plan developed by your predecessors?

Dr. Slavkin: The work of the Council in addressing the scientific opportunities for the Institute is part of our on-going process of reviewing research programs and directions. Many factors are considered in these reviews, such as the accomplishments of currently funded research, the state-of-the-science, the magnitude of the public health problem, and the capacity of our technology and research personnel. The plans of the past serve as a starting point for these reviews, with continual updating and revision. The participation of individual scientists from the extramural community has routinely been part of these activities.

SCIENCE EDUCATION

Mr. Porter: Dr. Slavkin, we know of your past interest in issues of science education at the pre-college level. Do you anticipate continuing your involvement in this area either in the Dental Institute or in crosscutting NIH science education efforts?

Dr. Slavkin: Yes! Throughout my professional life I have been engaged in pre-college education with particular emphasis upon inner city historically under-represented minority young minds. I plan to continue. The Carnegie Foundation's "Our Nation At Risk" in 1983 was a particularly sobering challenge for all of us to increase our engagement in pre-college science, mathematics, and health literacy. Unfortunately, in 1996 the need to improve K-12 science, math, and health education is even more urgent.

In my professional judgment, there are multiple levels for engagement within and between many federal agencies: 1) teacher enhancement programs to inform and equip K-12 teachers with the information and best pedagogy to nurture the developing thinking and values of our nation's young minds; 2) scientist/teacher partnerships in the classroom to enhance the what, why, and how of learning; and 3) scientist media communications to inspire, model, and inform the larger American public. In my opinion, each ICD as well as the entire NIH community can leverage limited resources to join in this national challenge. I personally plan on working closely with other ICDs and the Office of Science Education at the NIH, the National Science Foundation, and through the National Academy of Science and the Institute of Medicine. I strongly feel that the success of our nation is critically dependent upon a scientifically, mathematically, technologically, and health literate American citizenship.

RESEARCH CENTERS

Mr. Porter: Dr. Slavkin, your Institute has announced plans to support comprehensive oral health research centers. This mechanism has not been used before by the Dental Institute. Why did you decide this is the appropriate time to commit your resources to substantial centers?

Dr. Slavkin: Over the past four decades, the mission of the NIDR has been significantly advanced by the use of categorical centers to broaden the scope of dental research. With current new science opportunities, it is now apparent that most important human diseases require a paradigm that includes integration among behavioral, environmental, and biological sciences; for example, inherited craniofacial-oral-dental diseases and disorders, and acquired craniofacial-oral-dental diseases and disorders (i.e., emerging and re-emerging infectious diseases, neoplastic diseases, and chronic disabling diseases and disorders such as osteoporosis and related bone disorders, temporomandibular joint disorders, neuropathies, and neurodegenerative diseases). It is also evident that increased collaborations, partnerships, and leveraging funding are essential to maximize exemplary science and patient-oriented opportunities.

Therefore, it is the intent of the NIDR to develop in-depth "Centers of Discovery" encompassing a wide spectrum of coordinated efforts in basic, clinical, and applied research. It is also the intent of this Institute that these centers will include behavioral, health services, and clinical research; accelerate transfer of research findings to application by health professionals and the public and facilitate the development of marketable products; support demonstration research and outreach programs; and enhance the training of health professionals and the public concerning health promotion and the prevention, improved diagnosis, and treatment of specific oral, dental, and craniofacial diseases and disorders. The establishment of these centers represents a major effort to concentrate research resources within consortia that are the most capable of making a significant impact in these areas.

RESTORATIVE MATERIALS

Mr. Porter: Dr. Slavkin, do you have any progress to report on your Institute's support of work to create new materials for dental fillings?

Dr. Slavkin: We are supporting a project on the development of a non-mercury containing material at the Paffenbarger Research Center at the National Institute of Standards and Technology (NIST). The research is nearing the beginning stages of clinical application testing. We will keep the Committee informed of future development and progress.

MINORITY HEALTH

Mr. Bonilla: I have been following your initiative to develop a series of Regional Centers for Minority Health. What progress has been made in this effort?

Dr. Slavkin: The Institute has funded four Regional Centers for Minority Oral Health, which are co-located at New York University College of Dentistry and Forsyth Dental Center; UCLA School of Dentistry and Charles R. Drew University of Medicine and Science; University of Medicine and Dentistry of New Jersey and University of Connecticut School of Dentistry; and Meharry Medical College and the University of Alabama at Birmingham. Projects at the centers are focused on the prevention and treatment of orofacial diseases and conditions that occur with greater incidence in minority populations. They include research involving the clinical and molecular biology of wound healing following orofacial trauma and repair, studies of the biology and epidemiology of oral cancers, epidemiology and risk factor assessments of various oral conditions such as periodontal disease and caries, basic research relating to the biological causes of caries, the development of new dental biomaterials, studies of the causes and prevention of baby bottle caries, and studies of the sociological factors that influence whether or not members of the African-American community will participate in clinical research.

Mr. Bonilla: Have any of the Regional Research Centers on Minority Oral Health turned their attention to the needs of Hispanics?

Dr. Slavkin: Two of the centers, New York University and University of Medicine and Dentistry of New Jersey, are studying oral-dental-craniofacial health in Hispanics. In addition, the Institute is currently working with two potential applicants for future programs that will focus exclusively on the oral-dental-craniofacial health in various subgroups of Hispanics.

Mr. Bonilla: What is the NIDR doing to advance health promotion and disease reduction in the historically underrepresented minority populations in this country?

Dr. Slavkin: NIDR is supporting a demonstration research project in a predominantly African-American community in North Carolina. This project encourages the empowerment of the community to take charge of improving the oral health of its members. A working group of community leaders, the health department, and a community college will be partners with the Research Triangle Institute and the University of North Carolina in identifying critical concerns regarding oral health and undertaking initiatives to reduce risks and improve oral health. The research will evaluate the process and measure changes in behaviors and oral health status.

NIDR analysts are currently exploring the relationship between poverty status and a broad spectrum of clinical parameters of oral health, access to third-party payment sources for dental care, actual receipt of recent dental care, and perceived unmet oral health care needs. These analyses are being carried out for three major study populations: 1) children and youth 2-17 years of age; 2) adults 18-64 years; and 3) persons 65 years of age and over. To date, a number of major analyses of poverty status and oral health have been completed.

TMJ DISORDERS

Mr. Bonilla: Have you made any progress or made any advances in temporomandibular (TMJ) disorders?

Dr. Slavkin: NIDR-supported research has shown that a substantial subgroup of patients with TMJ disorders have osteoarthritic changes in the TMJ that are reflected by changes in biochemical markers in synovial fluid from the joint. We are now learning that such patients can benefit from more extensive use of pharmacological treatments, including anti-inflammatory agents.

In other research, scientists have discovered that experimentally produced inflammation in the TMJ and surrounding deep tissues is, as compared with cutaneous stimulation, more likely to lead to referred pain and persisting central neuroplastic changes. Also, better animal models have been developed for measuring pressures occurring on structures within the joint during functional activities such as chewing. These findings can provide a better basis for evaluating load requirements for biomaterials considered for use in the human TMJ. In addition, findings from NIDR-supported studies suggest caution in the use of radiographic markers to assess degenerative changes in the TMJ or internal derangement of the TMJ, since many patients remain pain-free and preserve normal jaw function for extended periods despite radiographic abnormalities in the position of the disc within the TMJ.

NIDR issued a Request for Applications in FY 1995 to solicit grant applications focusing on the etiology and pathogenesis of temporomandibular disorders, and 36 applications were received. We expect to make 7 to 9 awards in FY 1996.

Also, NIDR and the NIH Office of Medical Applications of Research sponsored a Technology Assessment Conference on April 29 through May 1 of this year on the management of temporomandibular disorders. A total of 23 international biomedical, behavioral, and clinician researchers and dental practitioners made presentations about the major issues related to the history, epidemiology, diagnosis and current treatment of TMD, and possible future diagnostic and management approaches based on findings from molecular biology and tissue engineering. Presentations were made to a consensus panel of 15 outstanding scientists and clinicians. Five specific topics were addressed: 1) the clinical conditions classified as TMD and results of leaving these conditions untreated; 2) types of symptoms, signs, and other assessments providing a basis for initiating therapy; 3) effective approaches to the initial management of TMD patients; 4) effective approaches to managing TMD patients with persistent pain and dysfunction; and 5) most productive directions for future research. Among the conclusions reached by the consensus panel were the following:

- The majority of available data from clinical trials and studies do not support the superiority of any method for initial management of most TMD problems; therefore, most patients should receive initial treatment using noninvasive and reversible therapies.
- The most promising approaches to managing TMD patients with persistent pain and dysfunction may result from evidence-based practice (i.e., the combination of clinical training, experience, and critical synthesis of evidence from rigorous clinical research studies) and patient-

centered care. Relaxation and cognitive behavioral therapies are effective management approaches for chronic pain.

- Multidisciplinary collaborations among basic and applied scientists in combination with practitioners should be established to facilitate future advances in diagnosis and management of TMD.
- Professional education is needed to ensure proper and safe practice in managing TMD, especially in regard to pharmacological, surgical and behavioral approaches.

CLEARINGHOUSE

Mr. Bonilla: Please give us an update on the National Oral Health Information Clearinghouse recently established.

Dr. Slavkin: The National Oral Health Information Clearinghouse (NOHIC) targets the information needs of special care patients, persons with medical or disabling conditions that compromise their oral health, and health professionals. In its first year of operation, NOHIC's primary focus was on developing resources and publications, initiating inquiry responses, and introducing the clearinghouse as a new information service to the oral health and special care communities. In 1995, NOHIC built on this foundation, shifting emphasis to targeted outreach and promotion, with continued development of resources and materials.

Oral Health Database Expansion: The oral health database now contains over 1,600 entries on special care and general oral health. The database format is currently being adapted for the Internet and will be available by this summer through the NIDR World Wide Web Home Page. This will enable ready access to patient and professional education materials that are not found in traditional research databases.

Outreach Efforts: Outreach efforts have resulted in a collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases to educate patients and health care providers about the oral complications of diabetes. NOHIC's diabetes/periodontal disease patient guide is now distributed through NIDDK's National Diabetes Outreach Program, a nationwide patient education effort that stresses the importance of diabetic control in preventing complications. NOHIC is also cooperating with the Juvenile Diabetes Federation of New York on a similar effort.

In the area of temporomandibular disorders, tremendous professional and public interest resulted in an upsurge in requests for NOHIC's TMD materials. Notices about the availability of TMD information, placed by the clearinghouse in both the lay and professional press, contributed to the 6,200 inquiries NOHIC received on this subject in 1995.

Inquiry Response: NOHIC fielded approximately 10,000 inquiries in the past year. Dentists and other health professionals accounted for more than a third of these inquiries, which ran the gamut of special care interests and issues. Major areas of inquiry included TMD, oral complications of cancer treatment, and diabetes.

Materials Development: NOHIC expanded its subject inventory of database searches to 14 in 1995. Prepared on the basis of recurring requests, the searches address topics of particular interest to NOHIC's audiences, such as smokeless tobacco, dry mouth, oral cancer, oral health care for persons with disabilities, and oral implications of AIDS and HIV infections.

Over 20 resource lists for special care and oral health organizations were generated this year from NOHIC's organization database. Categorized by disease area, the lists direct patients to information and programs relevant to their condition. Six state resource lists of hospital- and university-based special care programs were also developed, with a goal toward a nationwide inventory of such programs.

MARKER FOR INSULIN-DEPENDENT DIABETES

Mr. Stokes: I understand that the Institute's scientists have developed a marker for insulin-dependent diabetes. Can you tell us what this development will mean for improving the quality of life for patients suffering from this condition?

Dr. Slavkin: Between 65 and 70 percent of newly diagnosed insulin-dependent diabetes mellitus (IDDM) patients have antibodies to a pancreatic islet protein, IA-2. Combining IA-2 with other diabetic markers can detect up to 90 percent of IDDM patients. What is particularly interesting is that antibodies to this putative marker of IDDM are present in individuals 5 or more years before the onset of clinically apparent diabetes. These findings give us considerable hope that we may be able to intervene therapeutically or by prevention in this symptom-free period. The possibility that the IA-2 protein might be used in a "vaccine" to induce immunologic tolerance and prevent the disease is under active consideration. While these approaches are still on the drawing board, and much more research is required, there is reason to be optimistic that findings resulting from this research will significantly improve the diagnosis, treatment, and perhaps prevention of IDDM.

NUMBER OF RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African-American and other minority research investigators involved in research under its purview?

Dr. Slavkin: This past year, NIDR has been proactive in developing new approaches for increasing the number of African-Americans and other minority investigators in research. The Institute continues to review the recommendations of the special initiative on recruitment and retention of minorities in oral health research. Staff identified 11 issues that have an impact on expanding the pipeline, enhancing and utilizing extramural training and career development opportunities, and forming strategic alliances with other organizations.

The following activities reflect a few of the Institute's accomplishments: 1) a Request for Applications was released soliciting applications for a combined DDS/Ph.D Institutional Dental Scientist Training Program, which should be particularly attractive to minority students; 2) staff are working with the National Center for Research Resources on publicizing the Minority High-School Apprentice Program among suitable high-school students and teachers with whom the extramural community has strong interaction regarding careers in oral health research; 3) staff have conversed with the National Institute of General Medical Sciences staff on inclusion of dental students in the Minority Access to Research Careers (MARC) Honors Program; and 4) the Institute has recently issued a Request for Applications from minority investigators at minority institutions titled "Collaborative Opportunities for Research on Minority Oral Health." This mechanism supports collaborative research between minority investigators at minority institutions (i.e., those with more than 50 percent minority students or faculty or those that serve predominantly minority populations) with investigators at research intensive institutions (i.e., institutions that received more than \$50 million or more than 200 NIH grants during FY 1994). The aim of the program is to provide minority scientists, located at institutions that traditionally

do not compete well for NIH funding, with the opportunity to work closely with scientists who are successful in obtaining NIH funding.

In another activity, staff were successful in encouraging the Presidents of the Hispanic Dental Association (HDA) and the National Dental Association (NDA) to attend a National Advisory Dental Research Council meeting. Both individuals have stated the importance of their presence at meetings of this nature and how they look forward to strengthening their relationships with NIDR. In October 1995, Institute staff conducted a "Grantsmanship Workshop" at the annual meeting of the HDA. A similar Workshop will be held in August 1996 at the annual meeting of the NDA.

Mr. Stokes: What efforts has your Institute undertaken to educate minorities on opportunities that are available in biomedical research?

Dr. Slavkin: The Division of Intramural Research has continued its effort to attract the best young scientists to our training programs. We have placed particular emphasis on recruitment of minorities and women. The DIR continues a very active Summer Student Research Program, which in recent years has enjoyed particularly high participation by minority students (up to 50 percent). Through this effort, a large number of young minority students have been exposed to, and viewed first hand, biomedical research in action.

In the Division of Extramural Research, staff have developed a number of "listservs" to facilitate the exchange of information related to specific research areas. This information has been shared with participants at conferences, meetings, and symposia. It also has been announced in several minority newsletters.

Additional activities on outreach include a mass mailing to the MARC Program Directors about NIDR's short-term research training programs for minority and women dental students and informing them about research supplements available for minority students.

In an effort to increase minority elementary school children's interest in science and encourage them to pursue careers in math and science, a number of NIDR professional staff members have been participating in the NIH Science Alliance program. Staff are released during work hours so they may participate in hands-on, experiential type of science education demonstrations at local elementary schools with high minority student enrollments. These demonstration sessions are planned and prepared by NIDR staff working collaboratively with elementary school teachers. The subject matter covered is selected based on science concepts being taught at specific grade levels, new and innovative concepts introduced by NIDR staff, or specific interests expressed by the students. The Science Alliance program provides a workbook for scientists and teachers with step-by-step instructions of demonstrations they may use to help them get started. Initial training is also provided to interested staff by the Science Alliance program to familiarize staff with hands-on, inquiry-based science education activities, methods, and concepts.

ACCOMPLISHMENTS IN ORAL CANCER

Mr. Stokes: What do you expect to accomplish with your new oral cancer research centers?

Dr. Slavkin: Support for the NIDR Oral Cancer Research Centers will provide a mechanism for accelerating and expanding research designed to prevent, detect, and treat oral cancers--malignancies for which the 5-year survival rate is one of the lowest of all major cancers. The multidisciplinary and collaborative nature of these centers should facilitate greater advances in this area than those that could be achieved by individual projects.

The programs encompassed in these centers are designed to determine the molecular events responsible for the initiation, progression, and metastases of oral neoplasias and to develop methodologies both for the prevention and early detection of oral cancer. New and important information will be acquired concerning the mechanisms by which normal cell regulation is abrogated with resultant uncontrolled cell growth. Emphasis will be placed on genetic predisposition to oral tumors as well as genetic mutations, gene products, and etiologic agents (e.g., viruses, tobacco products, alcohol) that are implicated in the conversion of normal cells to premalignant and, subsequently, to malignant cells. Ultimately, novel approaches including new chemotherapeutic strategies as well as those related to enhancement of biological modifiers, DNA repair, and the genetic manipulation of tumor suppression will be explored as potential therapeutic modalities.

Finally, NIDR anticipates that over the next decade we will achieve a measureable reduction in the prevalence of oral cancer, improved diagnostics, and significant advances in "smart" therapeutics.

Mr. Stokes: When will these center grants be awarded?

Dr. Slavkin: The grants will be awarded in September, 1996.

Mr. Stokes: How much is included in the FY 1996 budget request for the project, and how does it compare with FY 1995?

Dr. Slavkin: Up to \$750,000 is committed for each center for the first year, in which it is anticipated that two centers will be funded. If additional applications are of sufficiently high scientific merit, the National Cancer Institute is considering funding two additional centers. These centers are a new initiative and were, therefore, not included in the FY 1995 budget.

CRITICAL INJURIES

Mr. Stokes: What major progress is the Institute making in regard to the repair of injuries to the head and face, and in the development of new dental materials?

Dr. Slavkin: Trauma to the head, face, and teeth remains a major problem for health care. One of the clinical issues is to develop "smart" therapeutic solutions to complex craniofacial-

oral-dental injuries. This often means the repair of cartilage, bone, enamel, dentine, and the soft tissues of the face and oral cavity. The NIDR through directly supported research (research project grants, program projects, research centers, and intramural projects), as well as through partnerships with other ICDs and other federal programs, for example, has discovered a number of morphoregulatory genes (BMPs and CDMPs) that regulate cartilage and bone formation. These discoveries are currently being advanced toward patient-oriented dental and medical orthopedic studies of growth factors for the repair of craniofacial, dental, and skeletal tissue injuries.

We have also supported scientists who have discovered how to replace dentin tissue using these morphoregulatory gene products. In the near future, through coordinated collaborations with biotechnology and dental companies, relatively easy-to-use techniques will become available for dentists to regenerate human dental tissues.

MINORITY CENTERS

Mr. Stokes: I understand that the institute has funded four regional research centers for minority oral health. Specially, what institutions were awarded funding? Describe the scope of research they will be conducting.

Dr. Slavkin: The four centers are co-located at New York University College of Dentistry and Forsyth Dental Center; UCLA School of Dentistry and Charles R. Drew University of Medicine and Science; University of Medicine and Dentistry of New Jersey and University of Connecticut School of Dentistry; and Meharry Medical College and the University of Alabama at Birmingham.

Projects at the centers are focused on the prevention and treatment of craniofacial-oral-dental diseases and conditions that occur with greater incidence in minority populations. These include research studies involving the clinical and molecular biology of wound healing following trauma and repair, studies of various oral conditions such as periodontal disease and caries, basic research relating to the biological causes of caries, the development of new biomaterials, studies of the causes and prevention of baby bottle caries, and studies of the sociological factors that influence whether or not members of the African-American community will participate in clinical research.

BIRTH DEFECTS

Mr. Stokes: What is the Institute doing to lower the risk of birth defects affecting the head and face?

Dr. Slavkin: A birth defect of the head and face occurs approximately every 1 hour and 15 minutes. The cause of these often profound craniofacial malformations includes environmental as well as genetic factors. NIDR-supported scientists have identified a number of environmental risk factors that increase the prevalence of human craniofacial malformations including alcohol, maternal smoking, retinoic acid (vitamin A as used for cystic acne in teenage and young adult women), anti-convulsant medications, excessive radiation exposures, and possibly maternal folic

acid deficiencies prior to and during the first 3 months of pregnancy. In addition, NIDR-supported scientists are seeking to identify risk factor associated genes that increase cleft lip and palate prevalence as well as less common craniofacial syndromes using molecular epidemiological studies (e.g., the Lancaster Study) and a number of animal studies utilizing mouse strains that have a very high frequency of spontaneous facial clefting. So far, these scientists have identified a number of growth factors, their cognate growth factor receptors, and several transcription factors associated with craniofacial clefting.

CLINICAL TRIALS

Mr. Stokes: What are some of the institute's most significant clinical trials? What can you tell us this year that you could not tell us last year with respect to the results of these trials?

Dr. Slavkin: NIDR is in the final stages of awarding funds, using a cooperative agreement mechanism, to mount a multidisciplinary clinical trial addressing the health effects of dental amalgams in children. The general purpose of the trial is to investigate the possible relationship between low-dose exposure to mercury vapor from dental amalgam restorations and the occurrence of specific health conditions. To accomplish this the Institute is initiating a prospective, randomized clinical trial involving children from high risk caries populations needing restorative dental treatment with dental amalgam. The main goal of this clinical trial is to investigate the potential neurological, psychological/behavioral, renal, endocrine or other relevant organ system effects that may be attributable to exposure to amalgam restorations. As this is a longitudinal study, results are not expected to be available for another 5 to 7 years.

A clinical trial on dental implants is in its beginning stage. It involves a comparison of two types of implants in terms of their longevity. The enrollment phase has been recently completed. A 5-year follow-up period is planned before results will be available.

Another trial involves the comparison of speech in children following one of two surgical approaches to repair cleft lip and palate disorder. This trial is in its initial stages and enrollment has just begun.

Given the relative scarcity of studies regarding the effectiveness and efficacy of caries-preventive procedures in populations other than children, an investigation of the effectiveness of selected self-applied therapeutic agents in reducing the incidence of root and coronal caries is underway in an adult population residing in low fluoride communities in northern New England (Maine and New Hampshire) and Long Island, New York. This clinical trial is intended to evaluate the effectiveness of daily use of .05-percent neutral sodium fluoride mouthrinse in comparison with daily use of 1.1-percent neutral sodium fluoride gel in reducing root and coronal dental caries in adults. As of April 1996, more than 84 percent of 4,554 adult subjects enrolled at baseline in the study continue to be active participants. Final examinations after subject use of the product (active ingredient vs. placebo control) for a period of 48 months are scheduled to be completed by this summer.

Mr. Stokes: Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Slavkin: We estimate that \$5.8 million will be available in the FY 1997 budget for clinical trials, compared to an estimated \$5.7 million in FY 1996 and actual obligations of \$5.4 million in FY 1995 and \$5.0 million in FY 1994.

Mr. Stokes: What is the institute doing to ensure the appropriate enrollment of minorities and women in its clinical trials?

Dr. Slavkin: The Institute actively supports the NIH plan to ensure the inclusion of women and minorities in clinical trials in several ways. First, all reviewers are instructed about the NIH guidelines and are asked to assess, as part of the peer review, the extent to which applications are in compliance with these guidelines. Second, the Institute tracks the progress of funded grants and each year enters the number of women and minorities, including the subgroups, into a database. Program staff are aware of the guidelines and actively monitor progress in enrollment to ensure compliance with the guidelines. In the event that enrollment appears to be lagging, program staff contacts the grantee to ensure that s/he is aware of the requirements of the guidelines and to determine the steps that are necessary to meet the requirements. Finally, the Institute has conducted seminars at national meetings (e.g., IADR), at meetings of the RRCMOH directors, and at universities (e.g., at the University of Washington summer institute on clinical trials) on the requirements for the inclusion of women and minorities and their subgroups into clinical trials.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: For the diseases and disorders that are under the purview of your Institute, where are we now with respect to closing the gap in minority health? Specifically, what progress do you have to report to the subcommittee this year?

Dr. Slavkin: There are three areas of particular relevance:

1. Caries and Tooth Loss

This year NIDR released a comprehensive report comparing the oral health status of African-American, Mexican-American, and Caucasian persons. The Third National Health and Nutrition Examination Survey is the first nationwide health examination study in more than 20 years that includes an assessment of the oral health of Americans of all ages. (In this survey Caucasian and African-American refer to people of non-Hispanic backgrounds). In general, African-American and Mexican-American children had less favorable indicators of caries status. Although the amount of caries in their permanent teeth was roughly similar, African-American and Mexican-American children had more than twice as much untreated decay as did Caucasian children. Use of protective sealants on permanent teeth was three times as common in Caucasian children as in African-American children or Mexican-American youngsters. Since the early 1970's the prevalence of caries in the permanent teeth has declined over time in both African-American and Caucasian children by about two-thirds.

Race-ethnic group disparities are evident for indicators of the health of the primary dentition as well. Mexican-American children were least likely to be caries-free in their primary

(baby) teeth. Untreated decay in primary teeth was a major problem uncovered by the survey. Mexican-American and African-American children had higher percentages of untreated decay than Caucasian children.

African-American and Mexican-American adults had less restorative care than Caucasians. Caucasian adults had approximately twice as much coronal caries as did African-Americans and Mexican Americans. However, African-Americans and Mexican-Americans had substantially more tooth surfaces in need of treatment than did Caucasians, more decay in tooth roots, and more untreated decay in tooth roots. Mexican-Americans had a more favorable tooth loss pattern than Caucasians or African-Americans; they were least likely to be toothless and had more teeth on average than the other groups.

NIDR is conducting further analysis of the survey to improve understanding of socioeconomic and other factors that may be useful in targeting people at greatest risk of oral health problems.

2. Oral Cancer

Mortality rates from oral and pharyngeal cancer have been rising since the 1950's among African-American males reaching almost 100 percent higher than Caucasian male rates. These rates among African-American males may have peaked in the late 1980's. Literally, one American dies every hour of oral cancer. In marked contrast, among Caucasians and African-American women, mortality rates have been declining over time. These rates roughly correspond to tobacco use patterns over time by race-gender groups. NIDR jointly with the National Cancer Institute has recently completed field work for a study to determine why oral and pharyngeal cancer incidence rates among males in Puerto Rico are much higher than among U.S. males; the factors being examined include smoking, alcohol intake, viruses, genetic susceptibility, and nutrition.

Meanwhile, survival rates are significantly worse for African-Americans with oral and pharyngeal cancer than Caucasians, and have not changed over time for either group.

3. Epidemiology of Dental Caries in Minorities

Some progress has been made based on available baseline data, but over half of all children are still affected by caries. Much work remains toward meeting the Year 2000 objective of no more than 35 percent of all children 6-8 years old having caries in their dentition.

Caries in Adolescents

The NHANES III showed that about 66 percent of both African-American and Hispanic adolescents 15 years of age, and about 69 percent of Caucasian adolescents the same age, had one or more caries in their permanent dentition. The Year 2000 objective for 15 year olds is not more than 60 percent of adolescents having one or more caries. Only 30 percent of Mexican-American and 41.4 percent of African-American adolescents ages 12 to 17 had a totally caries-free dentition.

Untreated Decay: A Major Problem for African-Americans and Hispanics

The most currently available data from NHANES III revealed that a high percentage of both African-American and Hispanic children and adults had untreated coronal caries as compared to Caucasians. Mexican-American children had the highest percentage with untreated decay (62 percent), followed by African-American children (59 percent), and Caucasian children (41 percent). For adults, African-Americans had the highest number of untreated tooth surfaces (3.4) followed by Mexican-Americans (2.8) and non-Hispanic Caucasians (1.5). The pattern for untreated root surface caries was similar with African-Americans having the highest number of treated and untreated root caries (1.6) followed by Hispanics (1.6) and then Caucasians (1.1).

Periodontal Status

Generally, non-Hispanic Caucasians exhibited better periodontal health than either non-Hispanic African-Americans or Mexican-Americans. This advantage remained even after adjusting for age and gender distribution of the three groups.

Tooth Conditions

Both Mexican-American and African-American adults ages 18 to 74 had a higher percentage of severe tooth conditions (namely pulpal involvement or retained roots) that may benefit from treatment. The percentage of teeth or tooth spaces that may benefit from treatment ranged from 27.6 percent and 36.4 percent in adults 18 to 34 years old to over 52 percent among adults 55 to 74 years old.

Major Gaps in Use of Preventive Measures

Major gaps still exist for minority populations in terms of use of preventive measures for improved oral health. Use of sealants is much lower for African-American and Hispanic children 8 and 14 years of age than for Caucasian children of the same ages. In 1991, only 48 percent of African-American and 39 percent of Hispanic parents and caregivers used appropriate bottle feeding practices to prevent baby bottle nursing caries (the Year 2000 target is 65 percent). Hispanics and African-Americans (as compared to Caucasians) also have a lower percentage of children using oral care prior to entering a school program, a lower prevalence of children 2-17 years old who ever visited a dentist, and a lower percentage of adults 35 years or older who visited the dentist within the past 12 months (for preventive reasons). The use of professionally or self-administered topical or systemic (dietary) fluorides for people not receiving optimally fluoridated water could not be assessed for minority groups.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum. What are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Slavkin: The NIDR engages in a variety of outreach and public education activities aimed at communicating research progress and its implications for health, as well as research-based information about specific oral diseases and conditions. Our target audiences include patients and their families, the general public, and health care providers. We often enlist the help of professional organizations, patient advocacy groups, the media, educators, and others to reach our target audiences.

Significant ongoing activities include the development and distribution of educational materials for consumers and health care providers. Some of the consumer-oriented materials are translated into Spanish, and some are designed and written for low-literacy audiences. Most of the materials, which include brochures, posters, and videos, explain what we know about the causes, diagnosis, treatment, and prevention of specific oral diseases and conditions. Topics range from how to care for your baby's teeth to treatment of oral complications of cancer therapies.

NIDR is collaborating with the National Cancer Institute, Major League Baseball, and about 20 other sports and health organizations on an initiative to educate adults and children about the health risks of smokeless tobacco use. Initially targeted to role models, particularly professional baseball players, the campaign expanded to include college athletes; high school students, coaches, and teachers; elementary school students; and Little Leaguers and their coaches.

The NIDR-NCI smokeless tobacco initiative helped catalyze a new program, called the National Spit Tobacco Education Program (NSTEP). NIDR is a partner in NSTEP, which is headed by the nonprofit America's Fund for Dental Health, a partner in the NIDR-NCI initiative. This year, Major League Baseball adopted NSTEP as its official tobacco education program.

The Institute uses a variety of approaches to communicate with research communities and health care providers. These include exhibiting at selected meetings and conferences; publishing articles in trade journals (this year we initiated a new series of articles in the *Journal of the American Dental Association*); and hosting symposia, conferences, and other gatherings (last year we brought large groups of dental students, dental editors, and dental practitioners to NIH to learn about oral health research). NIDR publishes a digest of research advances and significant activities that is distributed to researchers, educators, and editors.

NIDR staff members appear on television programs and visit schools around the country (from elementary through dental school) to reach both professional audiences and the public. The Institute recently established a home page on the World Wide Web that offers information for researchers, the public, and practitioners. NIDR also maintains several electronic discussion groups on oral health topics.

Press releases and other media activities are another means of disseminating information to our publics. In addition, NIDR contributes to the various NIH and DHHS communications outlets (print, radio, and television).

Three years ago, the Institute established a clearinghouse to target the information needs of special care patients--those with medical or disabling conditions that compromise oral health--and their health care providers. The National Oral Health Information Clearinghouse (NOHIC) began with a focus on developing resources and publications and initiating an inquiry response operation. With this foundation in place, NOHIC shifted its emphasis in 1995 to targeted outreach and promotion projects, while continuing to develop its resource base. Major outreach projects this year focused on diabetes and periodontal disease and the oral complications of cancer therapy.

On most outreach and education projects, the NIDR collaborates with federal and private partners. This past year, the Institute collaborated with the Literacy Volunteers of America and the WIC (Women, Infants, and Children) program to educate parents and caretakers about how to prevent dental diseases in their youngsters. We worked with the American Diabetes Information Clearinghouse and other diabetes organizations to educate patients and health care providers about the importance of diabetic control for preventing periodontal complications of diabetes. We also worked with the University of Illinois at Chicago to educate parents about the benefits of dental sealants. These and other collaborations have enabled NIDR to maximize the impact of its outreach and education efforts.

Approximately \$2.3 million is included in the Institute's FY 1997 budget for outreach and public education programs; this is the same amount as in the previous 3 years.

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account. Is this the case in your Institute? If yes, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Slavkin: It is true that the majority of these programs are funded in the research management and support account in NIDR, with some funding within the intramural research line and via contracts. By making reductions in other areas of the research management and support account, we believe we will be able to maintain our outreach and public education activities.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Slavkin: In FY 1995, the Office of Research on Minority Health (ORMH) provided supplemental funding of \$60,000 for three activities pertaining to a Regional Research Centers on Minority Oral Health (RRCMOH) initiative. Funding from ORMH enabled NIDR to schedule two annual meetings of the Centers' Directors and a Grantsmanship Workshop for minority faculty of the Centers. The meetings and workshops were held in Bethesda. The Directors' meetings addressed a number of administrative issues as well as issues on increasing minority participation in clinical trials, collaborating on research projects, and developing

outreach activities in science education for K-12 children and beyond. The workshop topics centered around grant writing skills, development of specific research ideas, and appropriate support mechanisms.

The ORMH also provided \$1,500,000 in FY 1995 for support of the Oral Health Supplement to the HIV Cost and Services Utilization Study (HCSUS). These funds represent full funding for the 4-year supplement, which extends from September 1995 through February 1999. The HCSUS core study, the most comprehensive research ever undertaken of HIV/AIDS care in the United States, is funded as a 5-year \$15 million cooperative agreement by the Agency for Health Care Policy and Research. People with HIV disease suffer from many oral complications that can cause pain and compromise their overall health status and nutrition, but little is known about these complications especially from a national perspective. ORMH funding for the Oral Health Supplement is supporting a comprehensive study of the oral symptoms, conditions, oral health needs, access, utilization, and costs of oral health services and provide much needed answers to address the oral health concerns of people, especially minorities with HIV disease nationwide.

Mr. Stokes: Are there specific projects that are co-funded by the institute and the office, and if so, why and which are they? Also, for the record, include their period of performance, and the percentage and amount of funding provided by the institute and the office.

Dr. Slavkin: No projects are co-funded by the NIDR and the Office of Research on Minority Health.

DENTAL IMPLANTS

Mr. Hoyer: A number of people are getting implants for missing teeth: from your perspective, what is the NIDR doing to improve these procedures especially when considering people are living longer than ever before. How long will these implants last?

Dr. Slavkin: When the NIDR was created in 1948, I was 10 years old. At that time the human life expectancy was approximately 55 years, and nearly one-third of all adult Americans were toothless. In the following 48 years the American life expectancy is now close to 80 years of age - nearly 32 million Americans are over the age of 65 years. Today only 10 percent of adult Americans have no teeth. These changing demographics reflect oral health improvements and the desire of mature and senior Americans who seek improved "quality of life" advances, including the retention of their own teeth, free of pain and discomfort, for their entire lifetime. In some of our American population missing several or more teeth, individuals seek and obtain dental implants to ensure a complement of teeth. Our challenge is to develop methods to augment dental bone to support dental implants, especially in an increasingly older population.

NIDR is addressing this challenge on several levels of complexity. We are investing in basic, translational, and patient-oriented research to develop molecular approaches to augment jaw bones in mature and more senior people. We are analyzing the long-term effects of periodontal diseases, osteoporosis, and other confounding conditions of bone that can compromise the success of dental implants. In addition, we have held a technology assessment conference related to dental implants and continue to provide optimal science transfer to the health professionals as well as the American public regarding the efficacy of dental implants. Finally, we are in the process of initiating increased efforts to develop new biomaterials for the replacement, regeneration, and/or repair of craniofacial-oral-dental tissues.

With respect to how long present day dental implants will last, we really do not know as yet with scientific evidence. Optimal dental implant success reflects a number of issues: 1) Are they designed and fabricated so as to be functionally capable of bearing the required physical "loads"? 2) Are they biocompatible with the host tissues? 3) Do they osteointegrate into the existing host bone tissue? Failure of any one of these issues can produce a complete failure. At the moment, the precise "risk" or failure rate has not been established for long-term functioning dental implants over several decades of life.

CLEFT LIP AND CLEFT PALATE

Mr. Hoyer: What is the role of the NIDR in working on cleft lip and cleft palate?

Dr. Slavkin: The NIDR was created in 1948 as one of the first three Institutes at the NIH. Soon thereafter, NIDR began studies of craniofacial-oral-dental genetics including cleft lip, cleft palate, and other less common craniofacial syndromes that reflect facial clefting as well as malformations or dysfunctions in other parts of the body. These basic, translational, patient-oriented, and community research studies continue. The NIDR is the lead Institute in providing research toward reducing the prevalence of craniofacial malformations including cleft lip and

palate. Therefore, our role includes health promotion, disease prevention, and improved diagnostics and therapeutics related to cleft lip and palate.

Clefting of the lip and palate (CLP) is one of the most common craniofacial anomalies in the United States. There are more than 7,000 children born alive each year with CLP, a rate of about 1 in 500 live births. Prevalence of clefting is lower among African-Americans than among Caucasians. Clefts are predominately of genetic origin; over 250 genetically based syndromes exist that include cleft lip or palate as a feature of their clinical presentation. Epidemiologic studies have shown that: 1) facial clefts are more common in boys, and isolated cleft palates are more common in girls; 2) cleft lip and palate are more common in plural births than in single births; and 3) clefts are related to lower birth weight, prematurity, and higher infant mortality rates. There is also evidence from epidemiologic studies that some environmental factors also play a role in the etiology of CLP. Clefts are associated with influenza and fever in the first trimester and maternal drug consumption during the first trimester, particularly opiates, penicillin, and salicylates. Finally, there is some evidence of a relationship between advancing age of parents and CLP.

BIOMATERIALS RESEARCH

Mr. Hoyer: Are we making any progress in biomaterials research? Can you tell us about these efforts?

Dr. Slavkin: During the last 6 years, there has been increasing translation of the fundamental scientific discoveries related to cell structure and function to the targeted opportunities of tissue engineering and the development of biomaterials. This translational research has been termed "biomimetics" - - to translate or mimic basic biological discoveries toward applications to improve diagnostics and therapeutics. The NIDR currently supports a number of scientific research programs engaged in tissue engineering and biomaterials toward the development of "smart" strategies to create novel therapeutics for oral cancer, bone, and cartilage diseases such as those associated with TMD, birth defects, neurodegenerative diseases, dry mouth or xerostomia, immune deficiency diseases and opportunistic infections, and periodontal diseases.

TMJ DISORDERS

Mr. Hoyer: Have you made any progress or made any advances in temporomandibular (TMJ) disorders?

Dr. Slavkin: NIDR-supported research has shown that a substantial subgroup of patients with TMJ disorders have osteoarthritic changes in the TMJ that are reflected by changes in biochemical markers in synovial fluid from the joint. We are now learning that such patients can benefit from more extensive use of pharmacological treatments, including anti-inflammatory agents.

In other research, scientists have discovered that experimentally produced inflammation in the TMJ and surrounding deep tissues is, as compared with cutaneous stimulation, more likely to lead to referred pain and persisting central neuroplastic changes. Also, better animal models

have been developed for measuring pressures occurring on structures within the joint during functional activities such as chewing. These findings can provide a better basis for evaluating load requirements for biomaterials considered for use in the human TMJ. In addition, findings from NIDR-supported studies suggest caution in the use of radiographic markers to assess degenerative changes in the TMJ or internal derangement of the TMJ, since many patients remain pain-free and preserve normal jaw function for extended periods despite radiographic abnormalities in the position of the disc within the TMJ.

NIDR issued a Request for Applications in FY 1995 to solicit grant applications focusing on the etiology and pathogenesis of temporomandibular disorders, and 36 applications were received. We expect to make 7 to 9 awards in FY 1996.

Also, NIDR and the NIH Office of Medical Applications of Research sponsored a Technology Assessment Conference on April 29 through May 1 of this year on the management of temporomandibular disorders. A total of 23 international biomedical, behavioral, and clinician researchers and dental practitioners made presentations about the major issues related to the history, epidemiology, diagnosis and current treatment of TMD, and possible future diagnostic and management approaches based on findings from molecular biology and tissue engineering. Presentations were made to a consensus panel of 15 outstanding scientists and clinicians. Five specific topics were addressed: 1) the clinical conditions classified as TMD and results of leaving these conditions untreated; 2) types of symptoms, signs, and other assessments providing a basis for initiating therapy; 3) effective approaches to the initial management of TMD patients; 4) effective approaches to managing TMD patients with persistent pain and dysfunction; and 5) most productive directions for future research. Among the conclusions reached by the consensus panel were the following:

- The majority of available data from clinical trials and studies do not support the superiority of any method for initial management of most TMD problems; therefore, most patients should receive initial treatment using noninvasive and reversible therapies.

- The most promising approaches to managing TMD patients with persistent pain and dysfunction may result from evidence-based practice (i.e., the combination of clinical training, experience, and critical synthesis of evidence from rigorous clinical research studies) and patient-centered care. Relaxation and cognitive behavioral therapies are effective management approaches for chronic pain.

- Multidisciplinary collaborations among basic and applied scientists in combination with practitioners should be established to facilitate future advances in diagnosis and management of TMD.

- Professional education is needed to ensure proper and safe practice in managing TMD, especially in regard to pharmacological, surgical and behavioral approaches.

NATIONAL INSTITUTE OF NURSING RESEARCH

ALZHEIMER'S DISEASE

Mr. Stokes: With respect to Alzheimer's disease are there specific activities that are underway at the Institute, or collaborative efforts underway between the Institute and the National Institute on Aging, explain?

Dr. Grady: Nursing research supports basic and clinical studies of the neurobehavioral and cognitive effects of dementing disorders, such as Alzheimer's disease, including ways to assess and treat symptoms and improve behaviors. Strategies to improve sleep of both patients and caregivers are also being tested for their effect on fragmented nighttime sleep, decreased total sleep, and increased daytime sleep. Early findings of one study indicate that a behavior intervention performed by nursing home aides can significantly decrease the level of assistance needed by patients with dementia in dressing themselves and in other activities of daily living.

Preliminary findings regarding Alzheimer's disease patients in long-term care facilities' Special Care Units, managed by nurses, indicated that overall, patient behaviors are more constructive and less disruptive than those of patients in traditional nursing home units. Special Care Units also involve families in the care of patients. Other findings include a significant reduction in stress among the Special Care Unit nursing staff. Family members also expressed greater satisfaction with the overall care and patient environment.

In collaboration with the Aging Institute, the NINR is participating in a clinical trial of a cognitive intervention for older people, designed to preserve function and promote independent living. Another focus is family caregivers and their ability to manage the symptoms and needs of their ill relatives while trying to maintain their own lifestyles. Nursing research is developing interventions that will help ease the effects of caregiver burdens, which can compromise their mood, immune system, and productivity.

MINORITY RESEARCHERS

Mr. Stokes: What can you tell us this year that you could not tell us last year with respect to what the Institute is doing to increase the number of African American and other minority research investigators involved in research under its purview?

Dr. Grady: Our institute places considerable emphasis on minority research opportunities. From the time we were established at NIH in FY 1986 until now, we have supported the NIH minority research supplement program to help our minority colleagues in their development as independent, competitive investigators in nursing research. From FY 1989 through FY 1995, we have been among the leaders at NIH in the number of minority supplements funded as a percentage of eligible research funds. In all, we have funded 77 minority supplements.

The National Institute of Nursing Research is one of only three institutes and centers at NIH to initiate its own program of minority supplements to institutional National Research and Service Award training grants. We have funded 21 of these grants.

Mr. Stokes: What efforts has your Institute undertaken to educate minorities on opportunities that are available in biomedical research:

Dr. Grady: We have developed a minority outreach plan to actively promote NINR's research training supplement program for minority pre-and postdoctoral trainees. We provide mentoring and other assistance to those who have completed training supplements so that they can move into independent research positions. We work with minority organizations, such as the National Black Nurses Association, Inc., and the National Hispanic Nurses Association, and the outreach components of other national organizations, such as the American Nurses Association and the American Association of Colleges of Nursing, to inform the minority community about NINR research and research training opportunities. In addition, we convene small groups of experts in minority health research and research training to provide advice and consider the special needs of minority institutions.

The NINR also offers grantsmanship workshops to minority institutions and arranges hands-on experience, through the NIH intramural program, for minorities in experimental methods, laboratory techniques, statistical analyses and other aspects of biomedical and behavioral research.

OLDER WOMEN'S HEALTH

Mr. Stokes: Women make up approximately 60 percent of people age 65 and over and some 72 percent of people age 85 and over. What is the Institute doing to improve the health of older women?

Dr. Grady: The National Institute of Nursing Research improves the quality of life for all Americans by promoting healthy lifestyles and behaviors that will ease the effects of disease. One area of emphasis is the association of breast cancer with advanced age. We know that older women are less likely to adopt prevention practices, such as self exams and regular mammography screening. These women are also at higher risk for developing and dying from breast cancer. Since projections indicate an increase in the number of older women in coming decades, there is an even greater need to address the problems of breast cancer control for this population. Some of our activities in this area include collaboration with the cancer and aging institutes on an initiative to find ways to encourage more women in the older age group to use life-saving prevention methods that can detect breast cancer as early as possible; strategies that involve social and family influences, including use of younger women to encourage their older female members to screen

for cancer; and tests of whether an intervention, which combines certain aspects of the role of a community hospital oncology nurse and a geriatric case manager, can help influence older women diagnosed with breast cancer to seek appropriate treatment.

NINR's Intramural Clinical Therapeutics Laboratory (CTL), conducts research related to older Americans. One CTL research program which focuses on urinary incontinence and bacteriuria in the elderly, conducted a recent study of patients with acute hip fracture. The CTL also works with scientists in the National Institute on Aging to investigate the relationship between urinary incontinence, bacteriuria, and hypertension to test strategies of controlling these disabling conditions.

Another area of emphasis to improve the health of older women is to enhance their physical conditioning. Many older adults lack mobility, strength, balance, and endurance. This raises physical problems and can cause the loss of independent living and increase the risk of injury. A central issue in the care of older adults is to maintain and promote physical and functional health required for independent, active, daily living. The long term goal of this initiative is to stimulate further research on the efficacy and effectiveness of physical activity, conditioning, and exercise in improving the health status of older adults.

Our relationship with the Office of Research on Women's Health has always been a close one. We collaborate on an initiative to study decision making processes in women's health. In another cooperative effort called the Study of Women's Health Across the Nation, we are examining women in their 40's and 50's to obtain a clearer health and social picture of women as they age. These studies include women from diverse racial and ethnic backgrounds.

CLOSING THE GAP IN MINORITY HEALTH

Mr. Stokes: For the activities that are under the purview of your Institute, where are we now with respect to closing the gap in minority health? Specifically, what progress do you have to report to the subcommittee this year?

Dr. Grady: A strength of nursing research is developing and testing interventions that are responsive to the needs of different cultural and ethnic groups. A sampling of our research aimed directly at particular groups includes:

Given the increase in the number of older people in our population, along with the rise in the number of caregivers of elderly who are ill, it is imperative that we find ways to assist family caregivers with coping strategies to help patients remain independent as long as possible and to conserve their own way of life. A study of care giving practices of African American and Whites who care for older family members is assessing variations in such areas as assets, obligations, attitudes and use of formal care. The findings will yield data for development of interventions that can meet special needs of these two groups of caregivers.

Another study based in Hawaii examines the quality of life of elderly spouses or siblings of Japanese American men with Alzheimer's Disease. The central purpose is to identify predictors of how the care giving burden will affect the lives of the caregivers in such areas as social and emotional well-being and life satisfaction. This information will shed light on the types of interventions and service that are needed.

We have studies that address several minority groups at risk for delivering low birthweight babies. One study focuses on low income African American pregnant women, who are twice as likely to have low birthweight babies as Caucasians. When pregnancy is combined with poverty, the result can be devastating on the pregnancy itself and on the baby. Physical and psychosocial stress is thought to be an important factor. A social support intervention, involving emotional support and ways to increase self-esteem is being tested. Representatives from the black community are also involved. The ultimate goal is to improve the women's chances for a normal pregnancy and a healthy child.

A study called "Sister to Sister: The Black Women's Health Project," is designed to stop the surge of infection among inner city African American women of childbearing age. So far the study is showing early promise of communicating with this hard-to-reach population, with an impressive retention rate of participants in the study's early phase. Subjects are recruited from the family planning clinic of a women's health center in Newark, New Jersey. Techniques to use to avoid sex or assure that it is as safe as possible are discussed. A general seminar on women's health promotion issues, such as early detection of breast, uterine and cervical cancer, and the effects of substance abuse on the fetus, is also provided. The principal investigator on this project and her husband designed and tested an AIDS prevention model, which was selected by the Centers for Disease Control and Prevention to be distributed nationally for use as part of the curriculum for inner-city youth.

A project that seeks to promote healthy, full-term infants explores the health care needs of Hawaiian, Japanese, and Filipino pregnant women living in a rural, low-income district of Hawaii. These women, who frequently avoid prenatal care until late in pregnancy, put their offspring at special risk for serious health problems. NINR supported investigators are working with public health nurses, community peer groups, and native healers to design, test and operate a culturally sensitive prenatal care program to prevent low birthweight babies, who are at high risk for death, or physical and developmental problems.

Studies that address the Hispanic population include a study that explores weight management activities of Mexican-American, Black and Caucasian women. Almost 25 percent of women are overweight, and obesity is more prevalent in Hispanic and Black women. Little is known about this troubling threat to good health, particularly for the Hispanic women who rarely seek treatment. The effect of socioeconomic and cultural factors on weight need to be clarified so that culturally appropriate interventions can be devised.

Low income, inner city Hispanic women are at high risk for substance abuse and HIV infection that endangers their own and their children's lives. Our research is seeking ways to prevent Hispanic women of child-bearing age from adopting these risky behaviors. Currently, there are few drug prevention programs aimed at women, particularly ethnic minority women, such as Hispanics.

A study of a pain measurement scale has focused on young children following surgery. The "Oucher" scale consists of a series of photos of a young child's face experiencing five different thresholds of pain. The patient points to the photo that most reflects the pain level he is experiencing. The Oucher scale comes in three types, those with photos of either Hispanic, Black or White children. The ethnic specificity of the scale has been shown to help young children more accurately identify their pain.

OUTREACH AND PUBLIC EDUCATION

Mr. Stokes: Outreach and public education are a critical component to the research continuum, what are the most significant outreach and public education activities underway at your Institute? How much is included in the FY 1997 budget for the Institute's outreach and public education programs, and how does this compare with the funding level for FY 1996, FY 1995, and FY 1994?

Dr. Grady: Special attention is being given to conveying research information by means of computer networks, including Internet. Scientists and academicians are already using information networks to exchange research information. The NINR intends to take full advantage of expanded networking capabilities. Our home page on the World Wide Web will provide access to information about the NINR and health care research to a wide audience, including the general public.

The NINR public affairs emphasis at this time is on health care practitioners and professional organizations. We work closely with other NIH institutes, universities and professional societies to convey important findings to practitioners rapidly. For example, we collaborated with the National Institute of Child Health and Human Development to inform nursing practitioners of a change in techniques to prevent Sudden Infant Death Syndrome. An NINR newsletter to health care publications, professional societies and prospective and current grantees, provides information on ongoing studies and research findings. Our scientific staff also networks with other scientists at professional meetings and scientific symposia.

Approximately \$125,000 is planned for the FY 1997 public affairs program, the same amount allocated FY 1996. This represents a slightly lower amount than FY 1995 (\$137,000) and FY 1994 (\$140,000), because of the expectation of increased reliance on electronic communications, which saves on printing costs.

Mr. Stokes: In most of the Institutes, these programs are funded in the research management and support account. Is this the case in your Institute? If yes, have you been able to maintain these programs in spite of the funding reduction in this budget account?

Dr. Grady: Yes, public affairs activities are funded in the research management and support account at NINR. Our program has been maintained, although we have experienced a slight decrease in funding allocated to this area.

BASIC RESEARCH

Mr. Stokes: The NIH supports a strong program of basic research with promise for improved prevention and treatment of disease. What does the Institute do to help ensure that advances from basic research are translated into interventions that help to improve the quality of life for seniors?

Dr. Grady: Our portfolio links biological and behavioral research to address health problems, encompassing studies from the molecular levels on up to the human being. An example of early findings in the clinical research arena provides hope for prevention of recurrent stroke. Stroke patients usually have low endurance for exercise, although physical activity is thought to be important in the recuperative process. When patients with a moderate weakness on one side use an exercise bike regularly for 30 minutes, they improve their aerobic capacity and sensorimotor function, as measured by such factors as sensation, balance and awareness of body position. The exercise training also significantly improves the systolic blood pressure. Since evidence suggests that the level of elevated blood pressure during exercise is comparable to elevated blood pressure that can occur during daily activities, a lowered systolic level during exercise could ultimately mean a reduction in the risk of a future stroke.

OFFICE OF MINORITY RESEARCH

Mr. Stokes: What collaborative efforts are underway between your Institute and the Office of Research on Minority Health? Are there specific projects in your Institute that are funded totally by the office, and if so, why and which are they? For the record, provide a complete listing of the projects, the period of performance, and the amount of funding provided for each.

Dr. Grady: The NINR supports and continues to encourage research that targets minority populations and recognizes the need to increase the number of underrepresented minority scientists participating in nursing research. NINR has funded a number of outstanding students and investigators through the NIH's Minority Supplement Program and through its own institutional training grant minority supplement program.

The receipt of the Office of Research on Minority Health monies will provide for the support of additional outstanding minority investigators and staff who will be able to contribute to the enrollment of minority populations into the studies and to the collection and the analysis of culturally sensitive data. There are no projects that are totally funded by the ORMH. However, supplements to existing grants are supported by ORMH.

Mr. Stokes: Are there specific projects that are co-funded by the Institute and the Office, and if so, why and which are they? Also, for the record, provide a complete listing of these projects, including their period of performance, and the percentage and amount of funding provided by the Institute and the office.

Dr. Grady: The ORMH does not co-fund any specific projects with NINR. Instead, the ORMH provides funding for supplements to the projects NINR has already selected for funding.

The listing of projects for FY 1995 that ORMH provided supplemental funding, the period of performance, and the amount of supplemental funding include: Parental Role Attainment with Medically Fragile Infants, March 1, 1995 - February 29, 1996, for \$47,530; Preventing/Managing Chronic Illness in Vulnerable People, August 1, 1995 - July 31, 1996, for \$144,500; and Managing Uncertainty in Stage B Prostate Cancer, September 1, 1995 - August 31, 1996 for \$75,326.

Our plans for FY 1996 include funding four supplements for a total of \$360,380.

JUSTIFICATION OF THE BUDGET ESTIMATES

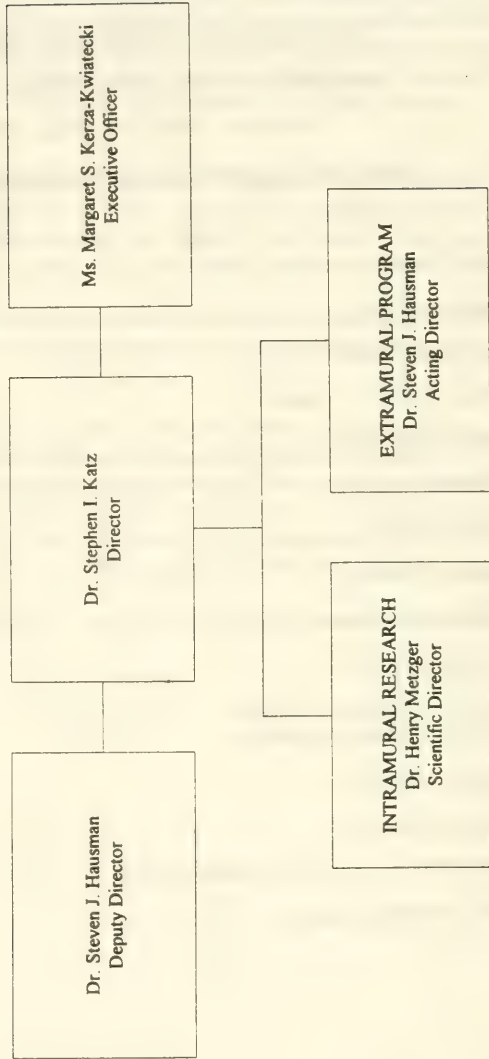
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to arthritis, and musculoskeletal and skin diseases, \$243,169,000.

Note—A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation	\$228,521,000	\$241,828,000	\$243,169,000
Reduction in accordance with P.L. 103-333	-142,000		
Rescission in accordance with P.L. 104-19	-203,000		
Subtotal, Adjusted Appropriation	228,176,000	241,828,000	243,169,000
Real Transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	-195,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities		-3,039,000	
Comparative transfer from: Other NIH Institutes for Management Fund adjustment . . .	141,000		
Subtotal, adjusted budget authority	228,122,000	238,789,000	243,169,000
Unobligated balance, lapsing	-44,000		
Total, obligations	228,078,000	238,789,000	243,169,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1995--\$2,914,000; FY 1996--\$4,000,000; FY 1997--\$4,000,000.

Also excludes funding for HIV/AIDS research activities: FY 1995- -\$3,879,000; FY 1997- - \$3,972,000, included in the NIH Office of AIDS Research.

Note: Excludes \$26,000 in FY 1995 and \$50,000 in FY 1996 for royalties.

Narrative Justification

National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
162	\$228,122,000	158	\$238,789,000	158	\$243,169,000	---	+\$4,380,000

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction. The NIAMS was created by Congress in April 1986. The occasion of the Tenth Anniversary of the Institute serves as a benchmark to assess our accomplishments as well as to identify current high priority research projects. Many stories of discovery and improved human health have been told over the last decade. In addition, research underway holds tremendous promise for the American public. Basic research is continuing to uncover many of the most fundamental mechanisms of life and is elucidating strategies for conquering clinical challenges. Clinical research and care are also improving dramatically. Research being supported by the NIAMS provides for better diagnosis and treatment, as well as ultimate prevention, of many of the most common, crippling, costly, and chronic diseases compromising life for the American people.

The NIAMS supports basic, clinical, and epidemiologic research, research training, and information programs on many of the more debilitating diseases affecting the American people. Most of these diseases are chronic and many cause life-long pain, disability, or disfigurement. They afflict millions of Americans, cause tremendous human suffering, and cost the United States economy billions of dollars in health care and lost productivity. These diseases include the many different forms of arthritis and numerous diseases of the musculoskeletal system and the skin. The Institute also conducts and supports research on the normal structure and function of joints, muscles, bones, and skin. These diseases affect people of all ages, racial and ethnic populations, and economic strata. Almost every household in America is affected in some way by arthritis, musculoskeletal diseases, or skin diseases. Selected examples of the ways in which NIAMS has approached these research challenges and opportunities are included in this document.

Annual Scientific Advances and Initiatives.

Osteoporosis. Osteoporosis is the leading cause of bone fractures in postmenopausal women and older people in general. It is characterized by low bone mass and microarchitectural deterioration of bone leading to skeletal fragility and an increased risk of fracture. The burden of health care costs due to consequences of osteoporotic fractures is estimated to be \$7-10 billion per year. One of the major goals of osteoporosis research is to identify people at a high risk for fracture before a fracture actually occurs. As new treatments for osteoporosis become available, it becomes increasingly important to assess both the current status of a person's bone mineral density and the response to treatment. A valuable technology is now available for patients with osteoporosis, quantitative ultrasound. Quantitative ultrasound is a technique for measuring bone mineral density and offers a faster, cheaper, and radiation-free alternative to other measures of bone mineral density for the assessment of osteoporosis. The ability of ultrasound measurements to discriminate those at higher risk of fracture will facilitate the targeting of individuals for preventive therapy.

The NIAMS continues to support a multi-pronged approach to osteoporosis, including research on basic bone biology, the Basic Osteoporosis: New Experimental Strategies (BONES) initiative (created by NIAMS, the National Institute on Aging, and the National Institute of Diabetes and Digestive and Kidney Diseases), treatment of calcium deficiency in young women, fluoride effects on fracture rate, genetics and bone density, the role of tamoxifen in bone loss and remodeling, and the national osteoporosis data group. Knowledge gleaned from these NIAMS-supported studies will provide important information that will help solve the osteoporosis puzzle.

A study recently analyzed the cost savings due to the fracture-sparing effect of estrogen replacement therapy. This analysis was based on a NIAMS study showing that estrogen reduced the relative risk of osteoporotic fracture. When the savings for 9,700 elderly women in the study population were extrapolated to all women in the United States age 65 and older who were taking estrogen in 1991, it was determined that the net savings in patient-care cost for that year amounted to \$333 million.

In other research related to osteoporosis, a clinical trial has been initiated by the NIAMS to determine the complementary and synergistic effects of exercise and hormone replacement on bone density and bone loss in postmenopausal women. The effect of a controlled exercise program on bone mineral density and body composition will be tested in postmenopausal women who are taking hormone replacement and those who are not. The results will provide helpful information for determining an overall bone loss prevention strategy for postmenopausal women.

Osteoarthritis. Osteoarthritis (OA) is the most prevalent acquired connective tissue disorder that affects the joints. It is characterized by joint pain, tenderness, and functional disability. OA and another type of arthritis, rheumatoid arthritis (RA), are major contributors to subsequent disability. Advances in diagnosis and treatment of this debilitating disease will have a significant societal and economic impact.

The association of OA with aging is significant. Radiographic evidence of OA is seen in at least 70% of the U.S. population over age 65, and in 80% of the population over 70 years of age. The number of Americans in this age range represents the fastest growing segment of the population, and is expected to reach 68 million people by the year 2020. Currently, elderly persons with arthritis visit health care providers twice as often as elderly persons with other chronic conditions. Yet, it is important to realize that OA is not just a medical problem for the elderly. Moderate to severe OA also affects significant numbers of young American adults. Projections are that, as the population ages, these numbers will rise to levels that could have a serious impact on the American public if better methods for prevention and treatment are not identified.

OA was the subject of a 1994 workshop sponsored by the NIAMS. An interdisciplinary group of leading clinicians and scientists defined the present knowledge of the etiopathogenesis of OA. This discussion facilitated the development of a broad array of cross-cutting research needs related to OA, including 16 specific recommendations for promising research. These directions for future research outline a series of basic science and clinical-epidemiologic studies necessary to better understand the causes of OA, and how most effectively to treat, and prevent, its development and/or progression. To help address some of these research priorities, the NIAMS issued a request for applications (RFA) and recently funded seven new research projects. Another initiative that NIAMS is pursuing related to this is the development of molecular markers for osteoarthritis. A challenge for clinicians and their patients is that it is difficult to detect (1) abnormal changes in the joint prior to the onset of symptoms of osteoarthritis that can be detected by x-rays, and (2) the subtle changes in disease progression or improvement with treatment. The development and validation of standardized, sensitive assays for disease-specific markers in body fluids or tissue specimens will provide an invaluable tool to permit early diagnosis and to detect subtle changes that occur with disease progression and the effects of surgical or pharmacological treatment. This methodology will also facilitate the generation of data on epidemiology and natural history of osteoarthritis. The NIAMS is launching a research roundtable on rheumatoid arthritis and osteoarthritis in FY 1997. This forum will allow dynamic interaction among the NIAMS, other NIH Institutes, other Federal agencies, the scientific community, industry, and voluntary and professional organizations involved with clinical research in rheumatoid arthritis and osteoarthritis. It will also identify potential opportunities for clinical interventions in osteoarthritis and rheumatoid arthritis.

Cellular and Molecular Mechanisms of Connective Tissue Repair. The repair of bone and connective tissues after damage from injury or degenerative disease is a long-standing problem of great significance and of interest to the NIAMS and the National Institute of Dental Research. Fractures of bone due to underlying osteoporosis, wounds of skin and oral tissues, damage to joint surfaces as seen in osteoarthritis, and injury to muscle, tendon or ligament all undergo natural repair to varying extents. However, insufficiency of natural repair is common, resulting in failure of fractures to bond, failure of wounds to heal, and persistent joint dysfunction. The introduction of biochemical and pharmacological agents or, in some instances, defined cell populations at the sites of connective tissue damage offers the potential for initiating and accelerating repair processes. To promote such interventions, the NIAMS and the NIDR will support efforts to: 1) identify critical repair functions in different tissues; 2) identify important

biological agents of repair processes; 3) characterize the molecular mechanisms by which such agents function in repair; 4) identify, isolate, and expand stem cell populations with the capacity to differentiate into the cell types involved in repair processes; and 5) develop techniques for the manipulation of various cell populations to facilitate repair processes.

Collagen, Tissue Remodeling, and Scleroderma. Collagen is a fibrous protein that is the major component of connective tissues such as tendons, cartilage, and skin. The collagen content of tissues is tightly regulated by synthesis and degradation. Failure to maintain an equilibrium between these two processes--called tissue remodeling collectively--leads to connective tissue disorders such as scleroderma, which is characterized by excessive deposition of collagen. A group of NIAMS-supported researchers recently introduced a mutation into mice that is designed to block the normal collagen breakdown that is part of tissue remodeling. Mice carrying the mutation grew normally for the first 7 months. Then they began to develop thickened skin and patchy hair loss due to skin fibrosis, resembling human scleroderma. The scientists subjected collagen taken from these mutant mice to a wide variety of tests; in so doing, they discovered a new cleavage site on the collagen molecule. They concluded that the newly discovered cleavage site permitted normal remodeling only during development and early postnatal life and that cleavage at the mutant site was necessary for subsequent remodeling of skin tissue. If similar mutations occur in humans with scleroderma, this mouse model should provide a powerful tool for further investigating the dermal fibrosis found in scleroderma.

Rheumatoid Arthritis. Rheumatoid arthritis, a disease that has puzzled scientists and clinicians for decades, has a prevalence of over 2 million in the United States. It affects women predominantly, many in middle age. During the past year NIAMS-supported scientists gained new information that both sheds light on how the disease develops and holds promise for improved treatment. They uncovered evidence for the induction of rheumatoid arthritis by a protein fragment that is present in a bacterium. In laboratory experiments with cells grown in culture, the scientists found that cells in joint fluid from patients with early rheumatoid arthritis had strong immune responses to the bacterial protein fragment, but cells in joint fluid from normal subjects did not. The abnormal reactivity of cells in the joint fluid of early rheumatoid arthritis patients could play a significant role in the development of disease and this breakthrough may lead to new strategies for delaying progression of rheumatoid arthritis.

Researchers in the Intramural Research Program of NIAMS are continuing important research on bacterial cell wall-induced arthritis in two rat models. These two strains of rats differ dramatically in their responses to a number of stimuli, including those that induce arthritis that resembles rheumatoid arthritis in humans. Comparative studies of these two strains provide a very powerful approach to defining the mechanisms involved in inflammatory disease. In addition, investigators in the Intramural Research Program have begun a new study this year on clinical and therapeutic investigations of the rheumatic diseases. Patients with inflammatory arthritis of less than one year's duration will be closely studied to better understand the mechanisms involved in early inflammation and to determine prognostic factors associated with the course of the clinical disease.

Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE), or lupus, is an autoimmune disease that disproportionately affects women, especially African American women. Although the cause is unknown, research suggests that hereditary factors play a role. Striking advances in applied genetics have dramatically improved the pace of research by NIAMS-supported investigators for discovering the genes that contribute to lupus susceptibility, severity, and mortality. Using experimental animal models of lupus, investigators are uncovering the genetic factors involved. New mouse models of lupus develop only selected aspects of this complex genetic disease; that is, they develop characteristic immune abnormalities, but the kidney disease they develop is mild. Studies of these models help increase understanding of the disease and also suggest strategies for altering the course of the disease.

The identification of genetic risk factors in lupus could indicate which patients may potentially develop severe disease and therefore merit early, aggressive treatment. Recent studies yielded two such risk factors--absence of the C4a gene and changes in the Fc receptor gene. C4a and the Fc receptor are involved in removal of molecules known as immune complexes, which otherwise stay in the body and cause tissue injury.

In family studies of lupus, investigators examined three genes that are important for normal immunity. Their findings indicate that more than one gene may be involved in conferring susceptibility to SLE and emphasize the complexity inherent in identifying the genetic basis of the disease. The NIAMS has established a lupus registry and repository to study patients and their families in order to identify the genes that determine susceptibility to the disease.

In other approaches to lupus, the NIAMS, the NIH Office of Research on Women's Health and the NIH Office of Research on Minority Health are co-funding the first clinical trial on the safety of estrogens for women with SLE. At the present time, women with SLE are usually advised not to take any medications that contain estrogen in the belief that it will worsen their disease or cause problems with blood clotting. This leaves women limited options for contraception during child bearing years and for hormone replacement therapy during postmenopausal years. These studies will focus on the effects of oral contraceptives on disease activity in women with SLE and on the effects of hormone replacement therapy with estrogen and cyclic low-dose progestins in postmenopausal women with SLE. Many of the patients recruited for this trial will be minority women. The outcomes of this trial are expected to have a major impact on the treatment options, health, and quality of life for patients with SLE.

Autoimmunity. It remains a puzzle why, in some patients, such as those with rheumatoid arthritis and systemic lupus erythematosus, the body's own cells turn against the body, but important insights into this phenomenon of autoimmunity have been revealed. A number of arthritic and skin diseases in the mission areas of NIAMS have their origin in autoimmunity and research on this is integral to much of the Institute. Autoimmune diseases are at a critical juncture now as researchers have an enhanced ability to identify the normal cell components that are targets in autoimmunity. However, expanded studies are needed to identify causative agents or body constituents involved in autoimmune disease. A key research priority remains the elucidation of what causes autoimmunity and what causes tolerance. The phenomenon of autoimmunity is of keen interest to a number of NIH Institutes.

Scientists have recently identified a group of inherited genes, the major histocompatibility complex (MHC), as the single most predisposing factor for autoimmune diseases ranging from rheumatoid arthritis and lupus to insulin dependent diabetes mellitus and blistering diseases of skin such as pemphigus. Yet, in spite of this striking association and the abundant information about the structure of MHC molecules, mechanisms underlying their role in determining whether or not the body's own cells will be tolerated or attacked remain a mystery. The major histocompatibility complex may affect disease predisposition through several mechanisms. The increased capacity to predict the interactions between the major histocompatibility complex and small components of proteins called peptides, and the availability of methods to test for MHC involvement have provided new and challenging opportunities for identification and analysis of self and foreign peptides in the production of autoimmunity.

Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and pemphigus are associated with significant morbidity. Although mortality rates have been decreasing steadily over the last few years due to advances in the control of clinical manifestations, the treatments available are useful for symptom relief but have limited impact in ultimate disease outcome. Furthermore, the side effects of these treatments can be very serious. Better understanding of the causes of these diseases may lead to the development of better, and more specific therapies that are less toxic.

Other implications for autoimmunity have emerged in studies of two other diseases in the mission areas of the NIAMS. Although ankylosing spondylitis (arthritis of the spine) and Reiter's syndrome (infection of the urinary tract and eyes followed by arthritis) are rheumatic diseases that are symptomatically different, they share a genetic marker. In the 1980s researchers discovered that a small fragment of intestinal bacteria associated with ankylosing spondylitis mimics a portion of this genetic marker. Since then researchers have been trying to find out how such protein fragments may mediate disease. Recently, NIAMS-supported researchers synthesized a series of proteins that replicate fragments of bacteria associated with ankylosing spondylitis and Reiter's syndrome. They discovered that the proteins bind to the genetic marker. The researchers hypothesize that this binding alters the body's normal immune response, culminating in ankylosing spondylitis and Reiter's syndrome.

Fibromyalgia. Fibromyalgia affects seven times as many women as men. Recently, NIAMS-supported investigators used a new imaging technique to determine if cerebral blood flow is abnormal in women with this disorder. Women with fibromyalgia and normal controls underwent the brain imaging procedure, assessment of pain threshold levels, and psychological evaluation. The researchers found that women with fibromyalgia display significantly lower pain thresholds and significantly higher anxiety and depression scores. With regard to the brain scan, patients with fibromyalgia, compared with normal controls, were found to have significantly lower blood flow. These findings suggest that structures in the brain involved in pain perception may have a functional abnormality that accounts in part for lower pain thresholds. Such knowledge could help target better interventions for relief of this debilitating disease.

Total Hip Replacement. Statistics on implantation of medical devices reveal that fixation devices and artificial joints for musculoskeletal diseases account for 51% of all implants in the

United States. Of these, about 50% are for total hip replacement, which is performed on approximately 123,000 people per year in the United States. The goal of total hip replacement surgery is to relieve pain and to improve range of motion of the diseased hip. Since 1982, the number of total hip replacements performed annually has increased approximately 64%. The direct cost associated with total hip replacement is approximately \$22,000 per patient, for a total cost in the United States in excess of \$2.5 billion per year. Its economic impact is likely to grow given the aging of the population.

Deterioration of prosthetic implant materials is increasingly recognized as a major factor limiting the durability and longevity of total hip replacement. Revision total hip replacement is necessary when there is failure of the artificial joint over time. The results of revision surgery are not as good as the initial procedure. In addition, the total costs of the procedure and hospitalization are greater than the initial procedure (this is especially true if deep infection is the cause), and the potential risks to patients, and overall costs, are greater because of their older age and other conditions. The NIAMS sponsored a workshop on total hip replacement in December 1994 and the Institute will continue its efforts toward the goals of improving human health and reducing the economic burden of total hip replacement.

Exercise Physiology and Fitness. It is well known that enhanced physical activities have numerous beneficial health effects. Musculoskeletal fitness and physical activity protect individuals against over-exertion or strains, preventing dire consequences including low back pain, muscle tears, bone fractures, tendon ruptures, and other disorders. Physical activity at all stages of life builds strong muscles and bones, greatly delaying the onset of frailty as people age, and protecting against disorders like osteoporosis. Additionally, fitness lowers the risk for obesity, cardiovascular disease, and other illnesses. Despite this evidence, many Americans live a sedentary lifestyle. Much of our information is based on studies of men. Less is known about women, children, and adolescents. Recent surveys included in the Surgeon General's Report on Physical Fitness show that approximately one-fourth of the adults in the US are physically inactive. This prevents them from realizing the demonstrated benefits of physical fitness.

Recently, a possible link between skeletal health and physical fitness was identified with the finding that physically-active post-menopausal women, and physically-active elderly populations in general, have a higher bone mineral density. This finding is very important, as bone mineral density and bone mass decrease with increasing age, resulting in more fragile bones that are more easily susceptible to fracture.

There is not a strong scientific research basis for understanding how the body integrates molecular mechanisms to coordinate fitness in muscle, bone, tendon, and ligament. The NIAMS will continue to promote increased basic research related to exercise and sports medicine in order to gain improved knowledge about normative measures of musculoskeletal fitness. One focus will continue to be on developing exercise patterns to build muscle and bone strength for currently inactive people as well as world class athletes. It is important to promote exercise for inactive people that improves fitness yet does not seem onerous. While we know much about the vigorous regimens used by body builders and long distance runners, we have little experimental

evidence of how shorter, more focussed patterns of exercise can effectively build muscle and bone strength.

Low Back Pain: America has moved from mobility in the workplace to increasingly sedentary work styles. As work has moved to machines with computers providing an important foundation for many work arenas, there has been a concurrent increase in the occurrence of particular work-related injuries and conditions, including low back pain, repetitive motion disorders, and carpal tunnel syndrome.

With regard to low back pain, an estimated 70-85% of all people have back pain at some time in their life. Back pain is the most frequent cause of activity limitation in people under 45 years, the second most common reason for physician visits, the fifth-ranking reason for hospitalization, and the third most common reason for surgical procedures. About 2% of the work force have workers compensation back injuries each year. The costs of workers compensation related to low back pain continue to increase and the total annual direct cost rose from \$4.6 billion in 1977 to \$11.4 billion in 1994. Recurrence rate of low back pain is very high--one year recurrence rates have been reported ranging from 20-44%. Lifetime recurrences of 85% have been reported.

The status and future directions of low back pain were the subjects of a November 1995 workshop sponsored by the NIAMS and the American Academy of Orthopaedic Surgeons. This unique meeting brought together clinicians and basic scientists with an interest in low back disorders, facilitating a discussion of shared interests and cross-cutting research needs that could be addressed by current methodologies. The meeting focused on basic science and clinical issues and these experts developed recommendations for areas ready for study. The NIAMS intends to support a clinical study on low back pain under acute conditions. This research will fill an important gap in the field, as much of the present research base deals with chronic low back pain, and less is known about acute low back pain.

Repetitive Motion Injuries. "Repetitive motion disorder" describes a constellation of conditions that primarily affect the soft tissues, including the nerves (as in carpal tunnel syndrome), tendons, and muscles (as in tension neck syndrome). These conditions are common, are often insidious in their onset, and may or may not have relatively clear diagnostic criteria. In addition, their etiologies are multifactorial, with work activities often contributing significantly, but not solely, to their development or exacerbation.

The relationship of repetitive motion disorders to the work place is significant. In 1992, 60% of new occupational illnesses were associated with repetitive motion. The national rate of reported repetitive motion disorders has increased dramatically. The highest rates generally occur in industries with a substantial amount of repetitive work (for example, meat and poultry processing, automobile manufacturing). Recently, the Bureau of Labor Statistics has reported an increase in repetitive motion disorders in "safe industries," such as data entry jobs using a computer. In June 1994, the NIAMS co-sponsored a workshop with the National Center for Medical Rehabilitation Research of the National Institute of Child Health and Human Development, and the American Academy of Orthopaedic Surgeons. Nationally recognized

clinicians, scientists, and ergonomists met to identify research opportunities that could be addressed by current methodologies.

Duchenne Muscular Dystrophy. Duchenne muscular dystrophy (DMD) is an inherited disorder in which there is slow but progressive muscle wasting. DMD results from a defect in the gene that codes for a muscle protein called dystrophin. Scientists suspect that the muscle degeneration found in DMD is due to the abnormal calcium levels that have been observed in dystrophin-deficient muscle. To explore the possible role of dystrophin in regulating calcium movement within muscle cells, NIAMS-supported researchers used an animal model of DMD known as *mdx* mice. Like humans with DMD, these mice lack dystrophin. When the researchers inserted a gene for normal dystrophin into the *mdx* mice, they found that the muscle cells restored intracellular calcium levels to normal. These results indicate that dystrophin plays an important role in maintaining the appropriate levels of calcium--without which muscle degeneration occurs. This research also supports the potential use of gene therapy for the treatment of DMD.

Discovery of a New Signalling Molecule in White Blood Cells. Cytokines are molecules that are very important in regulating the growth and development of cells. This family of molecules includes hormones, such as growth hormone, which regulates body growth. Analogously there are cytokines that are critically important for the growth and development of immune cells. Understanding how these molecules transmit the signal to tell cells to grow and differentiate, therefore, is of great importance in biology and medicine. Investigators in the NIAMS Intramural Research Program discovered a key enzyme, Janus kinase 3 (JAK3), that transmits such a signal in lymphocytes. It was further found that a group of children with severe immunodeficiency of unknown cause turned out to have a deficiency of JAK3. This is an important research finding for several reasons. First, it underscores the importance of this class of enzymes on transmitting signals by cytokines; without this enzyme the immune system does not function properly. Second, based on this precedent, researchers will also screen new patients with milder forms of immunodeficiency to determine if they also have abnormalities in this pathway. Third, because JAK3 patients are normal other than for their severe immune abnormalities, the finding suggests that this enzyme will be a good target for designing drugs that could be used to treat autoimmune disease and transplantation rejection. Finally, although many children with inherited immune deficiency can be treated with bone marrow transplantation, some cannot. For these patients, scientists can begin to consider gene therapy to complement their abnormal JAK3 genes.

Psoriasis. Psoriasis is a chronic and sometimes life-long disease with a strong hereditary component. It affects several million people in the United States. The disease can range from a few small patches on the skin and scalp to almost total body involvement and can be incapacitating. Some patients have an associated arthritis. Many of the more severely affected individuals have significant interference with their activities of daily living and their ability to hold a job, and they incur significant expenses in treating the disease. The NIAMS and the National Psoriasis Foundation have sponsored several research workshops on the disease, resulting in the establishment of a national tissue bank where samples are collected from patients with hereditary forms of the disease. The National Psoriasis Foundation established this bank about two years ago and research using specimens submitted to the bank has resulted in the determination that, at

least in some forms of hereditary psoriasis, there is a gene located on a specific chromosome (17q). Investigators in other research laboratories looking at different groups of patients with severe and sporadic psoriasis have not found the same association. Further work is necessary to determine both the specific gene on the 17q chromosome that is associated with a predisposition to psoriasis in families with that association and to determine other genes that may be associated with the predisposition in families that do not show the 17q association. Once the specific genes have been isolated and their products determined, greater insights would be available into the pathogenesis of the disease. This can be expected to open new avenues for intervention and improve the treatment for psoriasis.

Wound Healing. The NIAMS and several other NIH Institutes have had an ongoing interest in wound healing in the skin with particular emphasis, in recent years, on the problem of chronic wounds that fail to heal. This area has been the subject of a number of emphases including a recent workshop and solicitations for research in this area issued by several Institutes at the NIH. The costs associated with chronic wounds have a major economic impact on the country and, as many of these wounds affect the aged population disproportionately, this problem will continue to grow as the population ages.

In 1995, the FDA, NIAMS, several other NIH Institutes, and outside professional communities with interests and expertise in this area agreed to collaborate to solve a particular research problem related to wound healing. They focused on the inability to compare various wound healing intervention studies to each other because of the lack of standardization of a control arm. This is important because the FDA must approve a true control arm for intervention trials. A collaborative effort has been undertaken to provide some standardization for intervention trials in the wound healing area that would be acceptable to the FDA. This will facilitate basic and applied studies as well as improve pharmaceutical design since it will be known in advance that FDA will accept the control arm of the study as appropriate.

Benefits and Impacts of Research. Diseases under the purview of the NIAMS are characterized as being costly, chronic, common, and crippling. Estimates of annual total costs are \$55 billion a year for arthritis, \$71 billion a year for musculoskeletal disorders, and \$7 billion a year for skin diseases. The chronicity of these diseases is reflected in the fact that many of them cause life-long pain, disability, or disfigurement. They are very common as almost every American household is touched by some form of arthritis or musculoskeletal or skin disease. Statistics reveal that 1 in 7 Americans has some form of arthritis; 1 in 2 older women will have a fracture due to osteoporosis; 4 in 5 Americans will have low back pain at some point in their lives; and 1 in 3 Americans has a skin disease. The crippling dimension of these diseases and disorders results in pain, disruption of family and social networks, lost productivity, and increased health costs.

A recently released report supported by the NIAMS and the CDC has estimated that by the year 2020, 59.4 million Americans will be suffering from arthritis. In 1990, an estimated 38 million Americans, 15% of the population, were affected by arthritis. By 1994, the number affected had grown to nearly 40 million. The most startling news from the study, however, involves the future. For the first time, US researchers have made projections about arthritis

prevalence in years to come and the news is not good. By the year 2020 the number of Americans with arthritis will increase by more than 57% from the 1990 estimates. In that time, experts project that arthritis will affect 18.2 % of the population, or almost one of every five people.

The economic implications of these projections are enormous. An additional 20 million people with this condition over the next 25 years will impose a tremendous burden on the American health care system. As the number of people with arthritis grows steadily in the coming years, and if no biomedical breakthroughs are discovered, there can be expected to be a significant increase in the number of visits to physicians, as people with arthritis currently make twice as many visits to a doctor each year as the national average. In addition, there will be increases in medications prescribed and taken for the condition and in hospital and nursing-home costs related to arthritis. A similar increase in work disability expenses can be expected as well.

This dramatic increase is due to the aging of the population, particularly the baby boom generation, which is now entering the prime years of arthritis onset. The impact of this increase can be expected to be far-reaching, with implications for government and business as well as millions of Americans affected by arthritis and their families. Given the scope of the projected impact of arthritis and other rheumatic conditions in the year 2020, collaborations among academics, voluntary groups, local, state, and national governments, and health care organizations should be maximized to use limited resources to address a common goal.

The key to addressing these projected increases lies in more research. Scientists are convinced that research could yield results in time to help prevent some new cases and blunt the staggering impacts projected. Research is also needed to identify preventive strategies, as well as seek ways to reduce disabilities.

In addition to the impact on our health care system, this projected increase in arthritis has implications for business as well. In recent years, many Americans have expected to work past the traditional retirement age. Already arthritis is the leading cause of disability in people over age 65. As the number of people in that age group increases, so too will the pressure to find ways to keep those people active in the work force as long as possible.

Significant progress has been realized over the last decade from the investment in research on arthritis and musculoskeletal and skin diseases. We are on the brink of discoveries that can revolutionize health care and the treatment of chronic illnesses. NIAMS-supported researchers are today uncovering important pieces of the research puzzle and are launching initiatives to take advantage of emerging areas of science. NIAMS research has ramifications for this generation and generations to come. We are indeed investing in the future health of our nation and American people of all ages and population groups.

Overall Budget Policy. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting

RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities. Also in accordance with NIH policy, a stipend increase of 2.2 percent has been included for research trainees.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants						
Research projects:						
Noncompeting.....	493	\$112,466,000	485	\$109,995,000	520	\$116,952,000
Admin. supplementals.....	(18)	965,000	(18)	965,000	(22)	984,000
Competing:						
Renewal.....	73	15,928,000	78	17,706,000	71	16,465,000
New.....	102	17,767,000	117	26,628,000	108	25,034,000
Supplemental.....	4	1,574,000	1	154,000	1	197,000
Subtotal, competing.....	179	35,269,000	196	44,488,000	180	41,696,000
SBIR/STTR.....	33	4,111,000	33	4,447,000	40	5,541,000
Subtotal, research projects.....	705	152,811,000	714	159,895,000	740	165,173,000
Research centers:						
Specialized/comprehensive.....	30	26,050,000	30	28,142,000	30	26,895,000
Other research:						
Research career programs.....	70	5,755,000	70	5,755,000	70	5,755,000
Cooperative clinical research.....		200,000		206,000		206,000
Minority biomedical research support.....		445,000		465,000		465,000
Other research related.....	15	1,326,000	15	1,656,000	15	1,656,000
Subtotal, other research.....	85	7,726,000	85	8,082,000	85	8,082,000
Total, research grants.....	820	186,587,000	829	196,119,000	855	200,150,000

Training:						
Individual awards:						
Noncompeting.....	19	523,000	28	890,000	29	982,000
Competing.....	29	713,000	8	274,000	6	204,000
Subtotal, individual.....	48	1,236,000	36	1,164,000	35	1,186,000
Institutional awards:						
Noncompeting.....	146	4,791,000	155	4,936,000	154	5,219,000
Competing.....	44	1,555,000	48	1,705,000	45	1,546,000
Subtotal, institutional.....	190	6,346,000	203	6,641,000	199	6,765,000
Total, training.....	238	7,582,000	239	7,805,000	234	7,951,000
Research & development contracts.....	21	5,469,000	21	6,881,000	20	6,695,000
Intramural research.....	FTE 78	18,238,000	FTE 78	18,560,000	FTE 78	18,949,000
Research management and support.....	84	10,246,000	80	9,424,000	80	9,424,000
Total.....	162	228,122,000	158	238,789,000	158	243,169,000
Clinical Trials.....		(8,191,000)		(8,661,000)		(8,920,000)

NOTE: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Changes	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research: Arthritis and musculoskeletal and skin diseases.....		\$183,357		\$193,969		\$199,594		\$210,805		\$214,796		+\$3,991
Intramural research....	82	17,259	69	17,803	78	18,238	78	18,560	78	\$18,949	--	+389
Research management and support.....	84	9,832	81	10,009	84	10,246	80	9,424	80	\$9,424	--	0
Subtotal, obligations	166	210,448	150	221,781	162	228,078	158	238,789	158	243,169	--	+4,380
Unobligated balance lapsing.....		39		44		44		---		---		
Total, Budget Authority	166	210,487	150	221,825	162	228,122	158	238,789	158	243,169	--	+4,380

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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Summary of Changes

1996 Estimated budget authority.....	\$238,789,000
1997 Estimated budget authority.....	243,169,000
Net Change.....	+4,380,000

	1996 Current Estimated Base		Change from Base	
	Pos. FTE	Budget Authority	Pos. FTE	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Research Program:				
a. Within grade increases.....		6,542,000		+79,000
b. Annualization of 1996 pay increases.....		6,542,000		+40,000
c. 1997 Pay raise.....		6,542,000		+143,000
d. Increase in Federal Employees Compensation Fund.....		6,542,000		+2,000
e. Payment for centrally furnished services.....		6,313,000		-54,000
f. Increased costs of laboratory supplies, materials, and other expenses.....		5,705,000		+97,000
g. Service and supply fund increase.....		5,705,000		+29,000
Subtotal.....				+336,000
2. Research Management and Support:				
a. Within grade increases.....		5,648,000		+97,000
b. Annualization of 1996 pay increases.....		5,648,000		+35,000
c. 1997 Pay raise.....		5,648,000		+128,000
d. Payment for centrally furnished services.....		2,515,000		-138,000
e. Increased costs of supplies, materials, and other expenses.....		1,261,000		+15,000
f. Service and supply fund increase.....		1,261,000		+13,000
Subtotal.....				+150,000

Summary of Changes (Cont'd)

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.....	485	110,960,000	+35	+6,976,000
b. Admin. supplements.....	(18)			
c. Competing.....	196	44,488,000	-16	-2,792,000
d. SBIR/STTR.....	33	4,447,000	+7	+1,094,000
Total.....	714	159,895,000	+26	+5,278,000
2. Research centers:	30	28,142,000	0	-1,247,000
3. Other research:	85	8,082,000	0	0
4. Training:	239	7,805,000	-5	+146,000
5. Research & Development				
Contracts:	21	6,881,000	-1	-186,000
6. Intramural Research:	<u>FTEs</u>			
a. Program Increase	78	18,560,000	0	+53,000
7. Research Management and				
Support:				
a. Program decrease.....	80	9,424,000	0	-150,000
Subtotal.....				+3,894,000
Total changes.....				+4,380,000

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Budget Authority by Object

	<u>1996 Estimate</u>	<u>1997 Estimate</u>	<u>Increase or Decrease</u>
Total compensable workyears:			
Full-time equivalent employment.....	158	158	--
Full-time equivalent of overtime and holiday hours.....	1	1	--
Average SES salary.....	\$114,665	\$117,933	+\$3,268
Average GM/GS grade.....	10.2	10.2	--
Average GM/GS salary.....	\$47,814	\$49,167	+\$1,353
Average salary, grades est. by act of July 1, 1944 (42 USC 207).....	52,772	54,355	+1,583
Average salary of ungraded positions.	N/A	N/A	--
Personnel compensation:			
Full-time permanent.....	\$6,092,000	\$6,257,000	+\$165,000
Other than full-time permanent.....	1,859,000	2,021,000	+162,000
Other personnel compensation.....	363,000	394,000	+31,000
Special personnel services.....	<u>1,591,000</u>	<u>1,729,000</u>	<u>+138,000</u>
Subtotal, personnel compensation.	9,905,000	10,401,000	+496,000
Personnel benefits.....	2,112,000	2,136,000	+24,000
Benefits for former personnel.....	173,000	175,000	+2,000

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

	1996 Estimate	1997 Estimate	Increase or Decrease
Travel and transportation of persons..	291,000	292,000	+1,000
Transportation of things.....	24,000	20,000	-4,000
Rent, communications and utilities....	345,000	340,000	-5,000
Printing and reproduction.....	101,000	98,000	-3,000
Other Services:			
Consulting Services.....	150,000	143,000	-7,000
Other services.....	984,000	980,000	-4,000
Purchases fr. Govt. Accts.....	10,576,000	10,538,000	-38,000
Operations & Maintenance.....	455,000	454,000	-1,000
Operations & Equipment.....	551,000	545,000	-6,000
R & D contracts.....	5,582,000	5,431,000	-151,000
Supplies and materials.....	2,309,000	2,262,000	-47,000
Equipment.....	1,307,000	1,253,000	-54,000
Grants, subsidies and contributions...	<u>203,924,000</u>	<u>208,101,000</u>	<u>+4,177,000</u>
Total.....	238,789,000	243,169,000	+4,380,000

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Administrative Costs

	<u>1996 Estimate</u>	<u>1997 Estimate</u>	<u>Change</u>
Personnel Compensation:			
Full-time permanent (11.1).....	\$6,092,000	\$6,257,000	\$+165,000
Other than Full-time permanent (11.3).	1,859,000	2,021,000	+162,000
Other Personnel Compensation (11.5)...	363,000	394,000	+31,000
Special Personnel Service (11.8).....	<u>1,591,000</u>	<u>1,729,000</u>	<u>+138,000</u>
Total Personnel Compensation (11.9).	9,905,000	10,401,000	+496,000
Personnel Benefits (12.0).....	2,112,000	2,136,000	+24,000
Benefits for Former Personnel (13.0)....	173,000	175,000	+2,000
Travel (21.0).....	291,000	292,000	+1,000
Transportation of Things (22.0).....	24,000	20,000	-4,000
Communications, Utilities, and Miscellaneous Charges (23.3).....	345,000	340,000	-5,000
Printing and Reproduction (24.0).....	101,000	98,000	-3,000
Consulting Services (25.1).....	150,000	143,000	-7,000
Other Services (25.2).....	984,000	980,000	-4,000
Purchases of Goods & Services from Government Accounts (25.3).....	9,277,000	9,274,000	-3,000
Maintenance of Bldgs/Fac. (25.4).....	455,000	454,000	-1,000
Maintenance of Equipment (25.7).....	551,000	545,000	-6,000
Supplies and materials (26.0).....	<u>2,309,000</u>	<u>2,262,000</u>	<u>-47,000</u>
Total.....	26,677,000	27,120,000	+443,000

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

SIGNIFICANT ITEMS IN THE HOUSE, SENATE, AND CONFERENCE
APPROPRIATIONS COMMITTEE REPORTSFY 1996 House and Senate Appropriations Committee Report LanguageItem

Osteoarthritis - The House in its report 104-209, page 72, stated: "...The Committee is aware that in the absence of a cure for osteoarthritis, total joint replacement has been successful in relieving pain, enhancing mobility and independent living for many people who would otherwise be substantially disabled. However, during its hearings, the Committee learned that wear-related failure of the replacements has become a prevalent problem. The Committee urges NIAMS to expand its investigation of new materials and the interaction of implant devices and tissue, and to create a better understanding of wear processes that can prolong the life of the implant."

Action Taken or To Be Taken

The NIAMS continues to place a high priority on research into the causes and treatment of osteoarthritis. The Institute has funded seven new research applications in response to a Request for Applications (RFA) entitled "New Horizons in Osteoarthritis Research." The NIAMS is also supporting a project on biomimetics--the biological modification of a substance--and total joint replacement. If successful, this technology could speed up the time required for a patient's body to "bond" to an implant, thereby reducing the incidence of one of the most common causes of failure. Also in fiscal 1995, the NIAMS held a workshop on the status and future directions of total hip replacement. Nationally recognized clinicians and scientists in the fields of orthopaedic surgery, epidemiology, rehabilitation and physical medicine, biomechanics and biomaterials, geriatrics, and rheumatology met to address key questions and to identify research opportunities.

Item

Low Back Pain - The House in its report 104-209, page 72, stated: "...The Committee commends NIAMS on its upcoming workshop on low back pain that will address future research needs to improve the understanding of this condition and the care of the patient. After the workshop, the Committee encourages the Institute to develop and disseminate its findings to the public and scientific community."

Action Taken or To Be Taken

The NIAMS sponsored a workshop entitled "New Horizons in Low Back Pain" in November of 1995. This workshop focused on epidemiological and clinical aspects of three major areas:

lumbar radiculopathy, idiopathic low back pain, and degenerative stenosis. A comprehensive research agenda for both basic science and clinical research was developed and plans are now being made to fund new research initiatives in this area. With support from the American Academy of Orthopaedic Surgeons and the NIAMS, information from this workshop is being compiled in a book that is due to be published this summer.

Item

Repetitive Motion - The House in its report 104-209, page 72, stated: "...The Committee is concerned about the rapid increase in the number of serious injuries being reported to the Bureau of Labor Statistics related to repetitive motion syndrome. In 1992 alone more than 300,000 occupational injuries were reported which were attributed to this problem. The Committee is pleased that the Institute sponsored a workshop on repetitive motion injuries in 1994 and encourages further research in this area during fiscal year 1996."

Action Taken or To Be Taken

The NIAMS will continue to support research on repetitive motion disorders and is active in efforts to stimulate additional meritorious research in this area. The NIAMS is exploring a number of research opportunities in this area, including such areas as investigating the pathophysiology of repetitive motion disorders, studies on the diagnosis of repetitive motion disorders, and clinical studies to define optimal therapy, rehabilitation, and prevention of the more common repetitive motion disorders.

Item

Lupus - The House in its report 104-209, page 73, stated: "...The Committee urges NIAMS to continue to support research aimed at furthering the understanding of the gender and ethnic related factors associated with the high prevalence of lupus in women and minorities."

Action Taken or To Be Taken

The NIAMS recently cosponsored, along with the NIAID, the NIDDK, the NINDS, and the NIH Office of Research on Women's Health, a conference entitled "Gender and Autoimmunity." This scientific conference focused on disease and gender associations, mechanisms in autoimmune disease and gender, and specific gender effects in autoimmunity. In addition, the Institute supported the establishment of a national registry for the study of neonatal lupus. This registry will help to answer questions about the origin and causes of heart abnormalities and other lupus-related disorders.

The NIAMS also began funding of a clinical trial on the "Safety of Estrogen in Lupus Erythematosus." This clinical trial will provide scientific evidence to support physicians' decisions about the safety of providing oral contraceptives and hormone replacement therapy to women with lupus.

Item

Fibromyalgia - The House in its report 104-209, page 73, stated: "...The Committee commends NIAMS for stimulating research on fibromyalgia by holding a scientific workshop and subsequently making a number of awards for research on this disabling disease. The Committee urges NIAMS to continue supporting research in this area in fiscal year 1996 and collaborating with other Institutes."

Action Taken or To Be Taken

The NIAMS remains committed to fibromyalgia research and is closely following the progress of the five grant awards that were recently made as the result of a RFA. In other efforts, the NIAMS is attempting to promote and stimulate additional research in this area by investigating opportunities to collaborate with other NIH Institutes. In addition, the NIAMS is also working with fibromyalgia researchers, neuroscientists, endocrinologists, and other investigators from throughout the country in an effort to develop topics and identify speakers for an upcoming scientific workshop. The Institute hopes to hold this workshop in mid-1996.

Item

Psoriasis - The House in its report 104-209, page 73, stated: "...The Committee encourages NIAMS to continue to support genetic research to determine which gene is the specific gene for psoriasis as well as to pursue research on the mechanisms that lead to the onset of this disease."

Action Taken or To Be Taken

The NIAMS continues to fund research grants which are investigating the causes and treatments of psoriasis. Research into the genetic basis of psoriasis remains a priority for the Institute and the NIAMS would welcome the opportunity to fund further meritorious grant applications in this area.

Item

Connective Tissue Disorders - The House in its report 104-209, page 73, stated: "...The Committee is pleased that NIAMS has recently conducted a consensus workshop on heritable disorders of connective tissue and encourages NIAMS to pursue the workshop's recommendations on new research opportunities in the field."

Action Taken or To Be Taken

The NIAMS continues to support a number of research projects related to such connective tissue disorders as epidermolysis bullosa and Marfan's Syndrome. In addition, the Institute plans to significantly increase research into the molecular and cellular mechanisms of tissue repair. This new research will look at a variety of factors that influence the tissue repair process, including

how materials produced by cells affect the repair process, which cell populations are responsible for the repair and how these cells perform their functions, and whether techniques can be developed that would enable us to facilitate the repair process.

Item

Alopecia areata - The House in its report 104-209, page 73, stated: "...The Committee is pleased that NIAMS cosponsored a research workshop on alopecia areata last year and looks forward to seeing how this workshop builds on the public/private partnership in basic research in search of a cure."

Action Taken or To Be Taken

The proceedings from a workshop on this disorder were recently published in the Journal of Investigative Dermatology, and the NIAMS continues to be fully supportive of research into alopecia areata. As a result of ideas generated by this workshop, the NIAMS plans to issue a program announcement for additional research in this area.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Appropriation	1997 Amount Authorized	1997 Budget Request
Research and Investigation.....Section 301	42§241	Indefinite	<\$230,984,000	Indefinite	<\$235,218,000
National Institute of Arthritis and Musculoskeletal and Skin Diseases.....Title IV Part C	42§285d	Such sums as necessary		Such sums as necessary	
National Research Service AwardsSection 487(D)	42§288	Such sums as necessary	7,805,000	Authorization is Pending	7,951,000
Total Budget Authority.....				238,789,000	243,169,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation</u>	<u>1/</u>
1987	\$106,733,000	\$140,225,000	\$129,475,000	\$138,713,000	
1988	132,089,000	154,632,000	153,867,000	147,679,000	
1989	158,244,000 2/	155,487,000 2/	161,244,000 2/	159,897,000	3/
1990	167,334,000 4/	171,673,000	171,688,000	171,250,000	5/
1990 Sequester				-2,320,000	
1991	176,080,000	191,397,000 6/	198,746,000	193,247,000	7/
1991 Sequester				-3,000	
1992	204,797,000	204,977,000	203,076,000	203,047,000	8/
1993	214,929,000	214,619,000	214,619,000	212,456,000	9/
1994	210,382,000	223,280,000	223,280,000	223,280,000	
1994 Rescission				-76,000	
1995 10/	228,413,000	227,021,000	229,021,000	228,379,000	11/
1995 Rescission				-203,000	
1996	235,428,000 10/	241,828,000	232,919,000 10/	241,828,000	
1997 10/	243,169,000				

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes funds for AIDS research and education (\$687,000).

3/ Excludes funds for AIDS research and education (\$673,000), for Gramm-Rudman-Hollings spending targets (\$1,943,000), and for the FY 1989 Procurement Reform Reduction (\$91,000).

4/ The 1990 request excludes funds for the National HIV program (\$1,254,000) proposed consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes enacted administrative reductions of \$431,000.

6/ Excludes funds for NRSA training, which is unauthorized.

7/ Excludes enacted administrative reductions of \$5,195,000.

- 8/ Excludes enacted administrative reductions of \$1,089,000.
- 9/ Excludes enacted administrative reductions (\$1,717,000), Salaries and Expenses reductions (\$441,000), Consultant Services reductions (\$5,000), and TB transfer (\$209,000).
- 10/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
- 11/ Excludes enacted administrative reductions of \$142,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Full-time Equivalent Employment (FTE)

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Office of the Director	49	45	45
Extramural Program	35	35	35
Intramural Research	<u>78</u>	<u>78</u>	<u>78</u>
Total	162	158	158

Average GS/GM Grade

1991.....	10.1
1992.....	9.6
1993.....	10.5
1994.....	10.1
1995.....	10.1
1996.....	10.2
1997.....	10.2

NOTE: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Estimate
ES-6.....	1	1	1
ES-4.....	1	1	1
ES-2.....	1	1	1
Subtotal.....	3	3	3
GS/GM-15.....	13	13	13
GS/GM-14.....	19	18	18
GS/GM-13.....	8	11	11
GS-12.....	17	17	17
GS-11.....	9	9	9
GS-10.....	1	1	1
GS-9.....	10	11	11
GS-8.....	5	6	6
GS-7.....	19	18	18
GS-6.....	8	8	8
GS-5.....	1	2	2
GS-4.....	7	6	6
GS-3.....	2	2	2
GS-2.....	3	2	2
Subtotal.....	122	124	124
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade.....	5	5	5
Senior Grade.....	0	1	1
Full Grade.....	2	2	2
Senior Assistant Grade.....	1	1	1
Assistant Grade.....	1	1	1
Subtotal.....	9	10	10
Ungraded.....	N/A	N/A	N/A
Total permanent positions.....	128	132	132
Total positions, end of year....	162	163	163
Total full-time equivalent(FTE) employment, end of year.....	162	158	158
Average ES level.....	4	4	4
Average ES salary.....	\$112,653	\$114,665	\$117,933
Average GM/GS grade.....	10.1	10.2	10.2
Average GM/GS salary.....	\$47,507	\$47,814	\$49,167

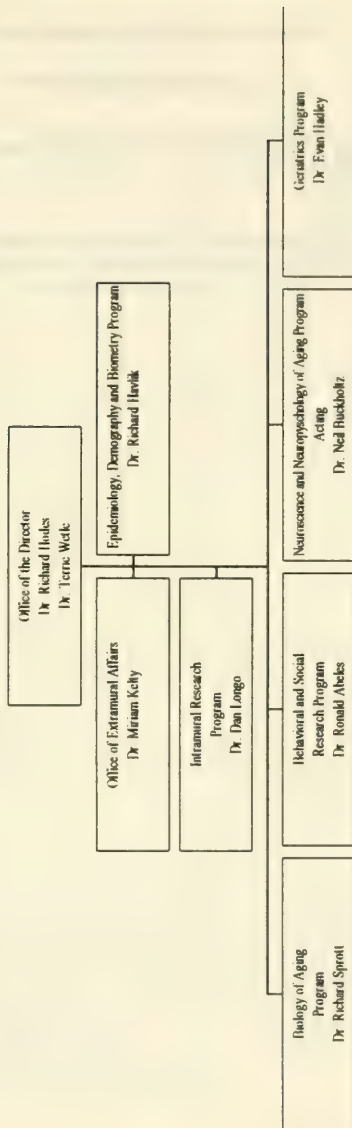
JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

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NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

For carrying out Section 301 and title IV of the Public Health Service Act with respect to aging, \$461,541,000.

Note--A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation	\$432,698,000	\$453,917,000	\$461,541,000
Reduction in accordance with P.L. 103-333	-375,000		
Rescission in accordance with P.L. 104-19	-332,000		
Subtotal, adjusted appropriation	431,991,000	453,917,000	461,541,000
Real transfer to:			
Other NIH Institutes through the NIH Director's one percent transfer authority	-369,000		
Comparative transfer to:			
Office of AIDS Research, NIH for HIV activities		-1,785,000	
Comparative transfer from:			
Other NIH Institutes for Management Fund adjustment	+542,000		
Subtotal, adjusted budget authority	432,164,000	452,132,000	461,541,000
Unobligated balance lapsing	-37,000		
Total, obligations	432,127,000	452,132,000	461,541,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1995--\$4,802,000; 1996--\$5,500,000; 1997--\$5,500,000.

Also excludes funding for HIV activities: FY 1995--\$1,715,000; FY 1997--\$1,824,000 included in Office of AIDS Research, NIH.

Note: Excludes \$21,943 for royalties in FY 1995.

Justification

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National Institute on Aging

FY 1995 Actual		FY 1996 Estimate		FY 1997 Estimate		Increase or Decrease	
FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
429	\$432,164,000	420	\$452,132,000	420	\$461,541,000	0	\$9,409,000

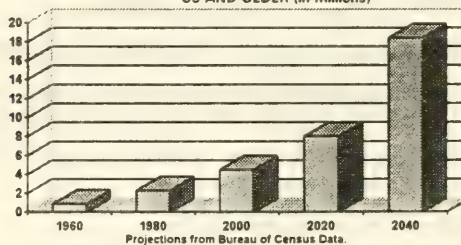
Overview

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute on Aging (NIA). Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Congress created the NIA in 1974 as part of the National Institutes of Health. At that time, aging research was in the early stages of developing ways to explore fundamental aspects of the aging process. Since then, knowledge about the fundamental processes of biology has grown as have new insights about the processes of health and disease in later years. The goal of NIA-supported research is to understand the basic mechanisms of normal aging and age-associated disease, disability, and other special problems and needs of the aged, and to translate this knowledge into treatment and prevention strategies.

An increasing interest in aging research is driven in part by a projected dramatic increase in the older population. People over age 65, who made up only four percent of the U.S. population in 1900, constitute approximately 12 percent now and will make up about 20 percent of the population by the year 2025. The over-85 age group, often referred to as the "oldest old", is the fastest growing segment of the older population. Population aging will become an important phenomenon of the next half century as the presently middle-aged "baby-boom" generation becomes eligible for Social Security and Medicare.

PROJECTIONS OF U.S. POPULATION:
85 AND OLDER (in millions)



Alzheimer's Disease

As the baby-boomers age and Americans continue to live longer, there is an increasing concern about Alzheimer's disease (AD), a devastating neurological disease which affects the cognitive function of sufferers who are primarily in the 65 and older age group. AD now affects an estimated four million Americans and is projected to reach critical proportions in the U.S. in the near future. Unless we can develop interventions to prevent or delay this dreaded disease, perhaps as many as 15 to 20 million older people and their families will experience the nightmare of Alzheimer's disease early into the 21st century. This is one reason that AD research continues to be a top priority for NIA.

Genetic researchers are encouraged by the identification of links between AD and genes on four chromosomes. Cases of familial Alzheimer's disease have been firmly linked to genes on chromosomes 1, 14, and 21, and the genes on chromosomes 1 and 14 have been identified and characterized over the past few months. In addition, a gene on chromosome 19 codes for apolipoprotein E (ApoE) a certain variant of which, ApoE4, has been implicated as a risk factor for AD. According to epidemiologic studies, the average age of onset of AD can vary by as much as 20 years depending on which variants of ApoE a person inherits. Further exploration of these findings to determine the exact function of these genes, how they interact, and their relationships to neuron function may lead to ways to develop effective treatments and ultimately decrease the occurrence of AD.

Physical Disability

Adding to the toll placed upon families and national resources by AD, physical disability is also a major factor in the over \$100 billion annually needed to cover the costs of long-term care for older Americans. NIA research has shown that through improved identification and understanding of risk factors and ability to predict disabling events, through the use of screening processes to identify target populations, and through the design and assessment of interventions individually tailored to reduce certain risks, disability can be prevented. Osteoporosis is a major risk factor for physical disability and we are making important progress in expanding our knowledge of it, progress that will lead to the development of new or improved interventions to prevent or reverse its destructive complications.

Even with the hope of major advances in the treatment and prevention of debilitating diseases, the demand for long-term care is expected to increase due to predictable demographic trends which are being studied by NIA-supported researchers. Research will be conducted on many aspects of long-term care, particularly on new and evolving forms of care with a goal of identifying the most effective and cost-efficient approaches.

Basic Biology of Aging

At an increasing pace, we are learning more and more about the basic molecular and biological processes and behavioral factors that underlie aging and their relationships to health and disease. For basic biological research, this knowledge is often gained through laboratory work involving cell cultures or subcellular extracts and provides the basis for the development of new or improved interventions to combat disability and disease. As one example, recent research on longevity assurance genes has significantly advanced our understanding of the genes and biochemical pathways involved in the regulation of longevity. NIA funded researchers have actually extended the life and/or health span of some lower organisms by incorporating these genes in their chromosomes. Once a better understanding of lifespan control in simple animal model systems is attained, researchers will be better able to study lifespan control in more complex animals and determine the relationship of these processes to aging, health, and disease.

Purpose and Method of Operation

The NIA funds research grants, contracts, and training awards through its extramural program, and operates its own laboratories through an intramural research program. Scientific direction and management is funded by the research management and support activity.

Overall Budget Policy

The NIA FY 1997 request is \$461,541,000, an increase of \$9,409,000 or 2.1 percent over the comparable FY 1996 level of \$452,132,000. In the FY 1997 President's Budget Request, NIA support for research project grants (RPGs) would increase by 2.6 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997 noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 263 competing RPGs and 981 total RPGs, an increase of 25 total RPGs over FY 1996.

Extramural Research

NIA funds a broad portfolio of research grants, contracts, and training awards encompassing many research fields and scientific disciplines. Although not all of NIA's research initiatives can be covered within this document due to space limitations, many high priority research areas are described in the following sections:

Declining Cognitive Function and Interventions for Older Adults

A major concern of older adults is thinking and remembering. A particularly exciting development is the rapid advance of neuroimaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), which permit researchers to study images of the brain while cognitive processing occurs. These and other techniques are relating learning and memory impairments to changes in brain structure and physiology, permitting a mapping of areas affected by Alzheimer's disease (AD) and other neurological disorders. This knowledge is valuable for detection, early diagnosis, and treatment of cognitive losses due to disease. Future research promises to identify the locations and processes of various components of memory and to differentiate the memory loss that can occur during normal aging to that which results from disease. Promising work has also produced interventions that can enhance some aspects of cognitive ability in older people. The NIA and the National Institute of Nursing Research are now soliciting grant applications for a trial to test such behavioral interventions in older adults of varying racial, ethnic, socioeconomic, and cognitive characteristics. The study should identify means of maintaining or increasing basic abilities critical for independence.

Alzheimer's Disease: A Decline in Cellular Communication

In AD, communication between nerve cells breaks down and leads to nerve cell dysfunction and cell death. AD destroys neurons in parts of the brain involved with cognition, especially in the hippocampus (a structure deep in the brain that plays an important role in memory encoding). As the hippocampal nerve cells degenerate, short-term memory falters, and eventually the ability to perform familiar tasks declines as well. AD also attacks the cerebral cortex (the outer layer of the brain). The greatest damage occurs in areas of the cerebral cortex responsible for functions such as language and reasoning. Emotional outbursts and disturbing behaviors appear with increasing frequency as the disease progresses. In the final stages, AD destroys the affected person's ability to recognize close family members or communicate in any way, leaving the person totally dependent upon others for care.

Prevalence and Costs of Alzheimer's Disease

An estimated 4 million Americans currently suffer from AD, and the lives of their caregivers are affected by this devastating illness. Families experience great emotional, physical, and financial stress. As the disease progresses and abilities steadily decline,

family members face painful decisions about the long-term care of their loved ones. Moreover, AD puts a heavy economic burden on society. One recent NIA-supported study estimated that the cost of caring for one person with advanced AD can be more than \$47,000 a year, whether the patient lives at home or in a nursing home. For a disease that can range in duration from two to 20 years, the overall costs of AD to families and to society are staggering.

Other factors in our changing society will compound the problem of AD in the near future. Life expectancy has been increasing since the turn of the century. Today in most industrialized countries, the 85 plus age group is the fastest growing segment of the older population and is also the segment of the population most devastated by AD, with an estimated 47 percent prevalence rate. These demographics emphasize the urgency of the need to find successful interventions that will delay or prevent onset of AD.

Genes in Early-Onset Alzheimer's Disease

AD can strike early and often in some families--and the disease in families such as these is identified as early-onset familial Alzheimer's disease (FAD). Studying the DNA of some of these early-onset FAD families, NIA-supported researchers have recently identified abnormalities in a gene on chromosome 21 in a subset of people with FAD. Over the last year, other investigators identified mutations in a gene on chromosome 1 in a set of families from Germany and mutations in a recently identified gene on chromosome 14 in other FAD families. The FAD genes on chromosome 1 and on chromosome 14 code for highly similar membrane proteins whose functions are not yet known. These mutated genes are responsible for very aggressive forms of FAD and may also play a role in the development of other types of AD. Further research on these mutations is expected to clarify key steps in the disease process. The FAD gene on chromosome 21 codes for an abnormal form of the precursor for amyloid protein, consistent with a role of amyloid protein in some forms of AD. Interestingly, people with Down's syndrome, who have an extra copy of chromosome 21, usually develop AD-like pathologies as they grow older.

ApoE4 and Alzheimer's Disease

In addition to the genes on chromosomes 1, 14, and 21 associated with FAD, the ApoE4 gene on chromosome 19 has been linked to late-onset AD, the most common form of the disease. Everyone has ApoE, a protein which helps transport cholesterol in the blood throughout the body. The gene coding for the production of ApoE occurs in three versions: ApoE2, ApoE3, and ApoE4. ApoE3 is the one most commonly found in the general population. ApoE2 may confer some protective effect against AD. ApoE4 is associated with greatly increased susceptibility to AD and earlier age of onset. It is found in many late-onset AD patients and is not limited to people with a family history of AD. On average, people with two copies of the gene for ApoE4 start showing AD symptoms before age 70 and are eight times more likely to develop AD than those who have two copies of the more common ApoE3 version. For those with no copies of ApoE4, the average age of onset is over 85.

Researchers have discovered that ApoE is localized in the two abnormal structures found in the AD brain: amyloid plaques and neurofibrillary tangles. Located outside and around neurons, these plaques contain dense deposits of amyloid protein. Neurofibrillary tangles are twisted fibers inside neurons. Progress continues to be made in determining the makeup of these abnormal structures and in elucidating the mechanisms that account for their buildup in AD.

The presence of ApoE4 in a blood sample does not necessarily predict AD. A person can have ApoE4 and not get the disease, and a person can get AD without having ApoE4. Because screening for ApoE4 would miss a large percentage of those who will develop AD and falsely identify others as future AD patients, widespread screening cannot presently be advocated. However, testing for the ApoE gene in combination with other tests, may soon contribute to the diagnosis of AD. The mechanism by which ApoE influences the risk of AD is currently under study. Scientists found marked differences in the rates at which ApoE3 and ApoE4 bind to critical nerve cell proteins involved in receiving signals from other cells, providing a potential basis for the influence of ApoE variants on the risk of AD.

While still controversial and far from proven, the hypotheses surrounding ApoE4 are driving new research. The relatively rare protein ApoE2 may protect people against the disease; it seems to lower risk and delay the age of onset. For instance, people with one ApoE2 gene and one ApoE3 gene have only one-fourth the risk of developing AD as people with two ApoE3 genes. If ApoE2 proves to be beneficial, then substances that mimic its effects might be candidate therapies to be tested for the ability to slow or prevent the progress of AD. Similarly further explanation of preliminary findings may lead to ways to reduce the effects of ApoE4, develop drugs to treat or prevent AD, and ultimately, decrease its occurrence.

Research on Dementia Special Care Units

Another line of AD research sponsored by the NIA concerns the effectiveness of special care units (SCUs), which are long-term care settings designed to meet the needs of people with AD and related cognitive impairments. The results of these studies may provide ways to improve care for these patients by determining the effectiveness of SCUs for their residents, the residents' families, and the unit staff members. This research also assesses the impact of SCUs on residents with and without dementia in non-specialized nursing home units. Research will define what constitutes "special care" and identify effective features of SCUs, including environment, staffing, activities, care planning, admission policies, size, and patient segregation. Preliminary results reveal how care in SCUs influences behavior, cognition, and physical functioning. For example, some of the most promising outcomes of SCUs are seen in the residents' quality of life as measured by increases in social behaviors and interactions.

Alzheimer's Disease Cooperative Study: Clinical Trials of Experimental Treatments

The Alzheimer's Disease Cooperative Study is composed of 35 research sites and was established to conduct clinical studies of promising drugs. This important work broadly complements other areas of AD research activity sponsored by the NIA such as the 27 NIA-funded Alzheimer's Disease Centers and an almost equal number of satellite centers. A study to assess the effectiveness of Deprenyl and vitamin E in slowing the course of AD began in October 1992; results from this trial should be available by mid-1996. Another study on drug and behavioral treatment of agitation began in June 1994 and is scheduled to end October 1996. A study of the anti-inflammatory drug prednisone to treat AD began in January 1995 and is scheduled to end in January 1997.

The latest trial, a pilot study investigating whether or not estrogen can improve function in women with AD who had previously undergone complete hysterectomy (with removal of both ovaries), was initiated in September of 1995. Previous reports suggested that post-menopausal women on estrogen therapy experienced benefits including improvements in mood, concentration, and memory. The major question addressed by this study is whether or not women with AD who had undergone prior complete hysterectomy show benefit from a twelve-month period of estrogen therapy. Study results should be available by the end of 1997.

Aging at the Cellular Level: Senescence, Longevity Genes, and Telomeres

The initial discovery that isolated mammalian cells have only a limited potential for continued cell division has provided an important paradigm for the study of aging and of cancer. Scientists think that this phenomenon, also known as cellular senescence, is a tumor-suppressive mechanism as well as an underlying cause of aging. Previously, the demonstration of cellular senescence was limited to an analysis of cells in culture. This year NIA-sponsored research has demonstrated that cell senescence also occurs in cells within live organisms. Additional efforts by NIA-funded researchers have resulted in the identification of specific genes involved in cell senescence.

Recent research on longevity assurance genes using invertebrate model systems, has significantly advanced our understanding of the genes and biochemistry involved in the regulation of longevity. Researchers have actually extended the life and/or health span of some lower organisms by incorporating these genes within their chromosomes. Once researchers gain a better understanding of lifespan control in simple model systems, they will be in a better position to study these processes in animals such as mammals, and to determine the relationship of these processes to aging, health, and disease.

Although it has long been known that cells in culture have a limited life span before proliferation ceases, the counting mechanism that determines this species-specific limit has been unknown. Somewhat akin to the plastic wrap on the end of a shoelace that prevents its unraveling and destruction, chromosomes have end structures known as "telomeres",

which serve to maintain the structural integrity and stability of the chromosome. A recent hypothesis is that telomeres shorten each time they are replicated during cellular division, and that continued cellular proliferation requires some minimal telomere length, yet to be defined. However, relationships among telomere shortening, cellular proliferative potential, and age-related disease remain to be clarified. Telomerase is an enzyme that functions to elongate telomeres, thus compensating for the telomere shortening which occurs with cell division. Cancer cells have been found to express relatively high levels of telomerase, thus allowing the cancer cell to replicate indefinitely. A more complete understanding of telomerase and telomere length regulation has the potential to elucidate approaches to delaying cell senescence as well as to prevent the unlimited replication of cancer cells.

Oxidative Damage, Antioxidant Defense, and Aging

"Free radical" damage has long been believed to be a risk factor for the degenerative processes which accompany aging in animal species ranging from insects to humans. Free radicals are byproducts of normal metabolism that are produced as cells turn food and oxygen into energy. To defend against these reactive and damaging molecules, cells have a multi-layer defense system including anti-oxidants that react with and neutralize the radicals which otherwise will damage proteins, membranes, and nucleic acids including DNA. Evidence continues to accumulate about the ubiquity of free radicals and their considerable destructive potential in living tissues. Recent NIA-funded studies demonstrated a strong inverse correlation between life span and production in the mitochondria (energy-producing powerhouses located within each cell) of reactive oxygen species, one particular form of free radicals. Thus, a promising aging intervention might be one which can increase the efficiency of the mitochondrial electron transport system.

Aging research in rodents has demonstrated that caloric restriction results in substantial increases in life span. Recent studies have shown that the extension of life span in mice by caloric restriction is accompanied by decreases in resting respiratory rate, mitochondrial generation of free radicals, and one type of damage in the mouse DNA, all of which are consistent with the hypothesis that oxidative stress is an important factor in aging. More research is needed to establish the critical relationships among free radical sources and the body's protective systems. An improved understanding of free radical processes may lead to the development of interventions (dietary, pharmacological, or genetic) for many of the diseases associated with aging and markedly increase healthy life span.

Nutrition In The Elderly

Recently, attention has focused on the nutritional status and nutrition-related needs of older individuals in this country. Researchers have indicated that a substantial proportion of Americans over the age of 50 have diets or diseases that place them at a high risk of malnutrition. Malnutrition can be either primary, which is defined by deficits in dietary intake or excesses (obesity, alcohol intoxication and various dietary imbalances)

caused by the diet alone; or secondary, which arises from other factors such as the presence of disease, special physiological states, or inborn errors of metabolism. In order to focus on the role of nutritional factors in preventing age-related diseases, it is imperative to define the alterations in nutrition and nutritional requirements which occur during aging and determine what interventions could be implemented to prevent or delay malnutrition. NIA will continue to promote nutrition-related research in order to improve our understanding of the interrelationships between nutrition, aging, health, and disease.

Melatonin and Sleep

There has been much recent publicity in the media about the potential effects of melatonin, including claims that this brain hormone can slow the human aging process, improve immune function, and scavenge DNA and protein damaging "free-radical" molecules. These claims unfortunately are unsubstantiated and controlled research is needed to confirm or deny them. However there is a solid base of data related to melatonin's role in the regulation of the body's circadian (day-night) rhythms and sleep, and it is possible that melatonin may act as an effective "hypnotic" agent for humans, able to induce sleep in both young and old individuals. Studies are underway to understand how melatonin affects the cells within the body's circadian clock, located deep within the brain. Melatonin appears to be a signal molecule telling the body that night is present; how it affects other systems in the brain and body requires further study. There is a need for continued research to determine potential interactions between time of administration and disruption of normal circadian rhythms with chronic usage, as well as possible other adverse health effects, and the delineation of what types of sleep disorders may be treated with melatonin.

Cardiovascular Disease, Vascular Stiffening, and Control of Hypertension

Cardiovascular disease remains a main cause of disability and the leading cause of death of older Americans, killing approximately 50 percent of those age 65 and older. Although age is the main risk factor for cardiovascular disease, the precise reasons are presently unknown. Continued research in cardiovascular and related fields is essential to ensure progress in defining important age-associated changes in the heart and blood vessels and in understanding the interactions between common age-related changes and the development of cardiovascular disease.

A potential risk factor that may underlie cardiovascular disease in the elderly is a stiffening of the large (e.g., the aorta) and medium-sized arteries. Age-associated vascular stiffening is accompanied by an increase in systolic blood pressure. In some individuals, vascular stiffening may become severe enough to lead to the development of isolated systolic hypertension. High blood pressure is the major risk factor for stroke and is also an important risk factor for coronary artery disease, heart attacks, and heart failure in older Americans. Since vascular stiffening has been considered a part of "normal" aging, treatment that may decrease arterial stiffness (e.g., lifestyle modification or pharmacologic intervention) is rarely advocated. NIA is conducting research to identify ways of

preventing and reversing vascular stiffening, such as exercise and other beneficial lifestyle changes. The potential benefit of preventing or reducing age-associated vascular stiffening is considerable, both in terms of cost savings and quality of life of older Americans.

Control of systolic hypertension now appears to be more important for good health than previously believed. A recent NIA-supported epidemiologic study has shown that high blood pressure in mid-life is a risk factor for cognition and memory problems in late life. As systolic blood pressure goes up, so does the risk of later cognitive difficulties. The study compared scores on cognitive tests given in old age with blood pressure readings taken up to 25 years before. Data from the study strongly suggest that early control of high blood pressure reduces the risk for cognitive impairment in old age.

Menopause, Osteoporosis, and Estrogen Replacement Therapy

Menopause, a universal phenomenon in women as they age, has been remarkably understudied. To rectify this situation, NIA, in collaboration with other organizations will continue to support the recently initiated multi-site, multi-discipline *Study of Women's Health Across the Nation (SWAN)*. This study will gather critical information on the chronology of the biological and psychosocial factors related to the menopausal transition and the effect of this transition on subsequent health and age-related disease. SWAN will generate extensive data on menstrual cycle characteristics such as markers of ovarian function, health and social characteristics, nutrition, ethnicity, reproductive history, risk factors for diabetes, hypertension and cardiovascular disease, and physical activity.

Osteoporosis and its consequences, particularly vertebral and hip fractures, are a significant cause of frailty, morbidity, and mortality in old age. An estimated 25 million older Americans are currently affected by osteoporosis. Each year, thousands of older Americans, more women than men, are admitted to costly long-care facilities due to hip fracture. NIA-supported osteoporosis research includes clinical studies of age-related bone loss and fracture epidemiology, intervention trials to prevent or reverse bone loss, and basic laboratory studies on the biology of osteoporosis and bone cell function. Results of studies are encouraging as to the potential for preventing bone loss and related fractures. For example, newly published results further indicate the benefits of estrogen replacement therapy. Estrogen use and bone mass were assessed in more than 9,000 older women to determine the association between estrogen use and fractures. Current estrogen use was associated with a decreased risk for many fractures when compared with no estrogen. Data from the study indicates that for optimal protection against fractures, estrogen should be initiated soon after menopause and continued indefinitely; additional studies are needed to confirm these findings.

Laboratory studies will continue to generate the knowledge base upon which new or improved interventions can be designed to prevent or reverse bone loss. One recently completed NIA-supported study was designed to determine the ability of parathyroid hormone (PTH) to restore lost bone in animals at skeletal sites with moderate and severe bone loss. The findings from this study indicate that: 1) PTH is much more effective than

antiresorptive agents in restoring lost bone in the estrogen-deficient skeleton, 2) treatments with antiresorptive agents and PTH have no additional benefit over PTH alone, and 3) PTH fails to restore the most severe states of bone loss. The latter finding may provide insight into the failure of some osteoporotic patients to respond adequately to agents such as fluoride or PTH. Further animal studies are needed to build upon these findings before initiating human studies.

Strategies to Prevent Disability in Older Persons

Disability among older Americans is a major contributor to the more than \$100 billion spent annually on long-term care in the U.S. Identification and reduction of risk factors in older people can make a critical contribution to quality of life and help prevent the disability that leads to long-term care. Recently completed studies typify NIA's approach to applying relatively simple, inexpensive technologies to prevent the complex and expensive problems brought on by disability. To identify older individuals with pre-clinical disabilities who may benefit from targeted interventions, NIA scientists have been evaluating functional assessment tests for use in screening. One such study of older non-disabled persons found that three short tests of physical performance abilities strongly predicted disability as much as four years in advance.

In another study, researchers conducted the first randomized controlled trial using the multiple risk factor approach to reduce falls in older people. The interventions targeted risk factors for falls, such as muscle weakness, postural hypotension, use of sedatives or multiple medications, and impairments of motion such as balance and gait. Participants received individualized treatment, including medication adjustments, strength and balance training, and instruction on safe practices to avoid lightheadedness and environmental hazards. Over a one-year follow-up period, the participants' rate of falls was reduced by nearly half compared to that of the control group which had received only social visits. The intervention was also shown to be cost-effective, particularly among individuals at high risk for falling. Since more than 250,000 hip fractures occur each year among persons over age 65, a substantial national cost savings should result from incorporating the tested strategy into the usual health care of older persons.

A four-year longitudinal study of women identified risk factors for hip fracture that allow targeting of very high-risk women for preventive strategies. There was a 25-fold difference in hip fracture rate between those women with two or fewer risk factors and normal bone density, and those women with five or more risk factors and low bone density. Maintaining body weight, walking for exercise, avoiding long-acting benzodiazepines, minimizing caffeine intake, treating impaired vision, and taking measures to maintain bone density are among the steps identified that may decrease hip fracture risk.

Older people often lose their independence and require long-term care after hospitalization for acute illnesses. In a recent study, older persons admitted to a teaching hospital for general medical care were randomly assigned to receive either usual care or special care including a carefully prepared environment, specific protocols for prevention

of disability and rehabilitation, and planning for the patient's return home. Without increasing in-hospital or post-discharge costs, the study showed that individuals who were helped to maintain or achieve independence in self-care activities were significantly more able than individuals receiving usual care to perform basic activities of daily living and less likely to need institutional long-term care at the time of discharge.

Elder-Friendly Environments

Human factors research adapts technologies and redesigns home and community environments to accommodate the sensory, motor, and cognitive abilities of older adults. This research results in devices and other components of the physical environment that better match the skill levels and abilities of users, helping to prevent injuries such as hip fractures, and remove physical and social barriers to independence. In addition to modifying structures to foster community access, this research targets design of kitchens, bathrooms, and security systems as well as medical devices, instructions, and labeling. Data from human factors research has already helped improve driving safety and product ease of use. Special emphasis is now being given to how older people use computers and other aspects of the office environment and new information technology as the U.S. workforce ages.

Health Behaviors and Behavior Change over the Life Course

Many of the problems of aging result from behaviors that place individuals at greater risk for poor health, depression, and other negative outcomes. NIA-supported research has documented the benefits for health and longevity of adopting healthy lifestyle practices, such as physical activity and nutrition, and terminating health-impairing habits, such as smoking, even at a very old age. These benefits and recommended steps for lifestyle changes have been well publicized. Nevertheless, surveys report that older people often are not motivated to make the desired changes. Additional research is therefore being stimulated on topics such as the social and behavioral factors involved in initiating and maintaining health-enhancing behaviors, the role of health care providers in identifying risk and encouraging positive self-care practices, and the design of regimens appropriate for older people in community and institutional settings.

As one example, numerous studies have documented the influence of exercise and physical activity on longevity, even among the oldest old. Recent studies are also showing the benefit of regular exercise in reducing costly hospital stays and nursing home admissions. Current research advances document the importance of the social and behavioral context when studying physical activity and exercise among older adults. There is a growing consensus that exercise programs, to be effective, must be tailored to older people's functional status, also taking into account older people's beliefs and readiness to adopt and maintain new exercise habits. Home-based physical activity programs supervised by telephone contact represent one promising strategy for reducing barriers to regular exercise experienced by caregivers with demanding care responsibilities.

However, more than half of older people are sedentary or under-active. For men and women aged 55-84, the primary reason for not exercising was "lack of interest." The remaining leading reasons given by older people for inactivity vary by gender; women specified not having an exercise companion as a major reason. Among the men and women older than 85, fatigue, imbalance, and concerns about falls were the primary reasons given for not exercising. Understanding the reasons older people give for limiting or avoiding many moderate and vigorous physical activities is a critical step in designing exercise programs that will actually be incorporated into older adults' daily routines.

Health, Work, and Retirement: Medicare, Technology, and Rising Health Costs

As lifespan and vitality in later life have increased, more and more older people are able and willing to work productively well into late adulthood. According to NIA's Health and Retirement Survey, almost three-fourths of American workers now would prefer to phase in their retirement with a gradual shift to part-time work rather than stop working abruptly. The economic cost of workers who retire for 25 percent or more of their lives is already creating a considerable social and financial burden that will increase when the baby boomers retire. One major goal of this research is to understand the potential represented by workers over age 60, especially for part-time engagement in the workforce.

NIA's research on the economics of health and retirement focuses on the determinants and implications of economic well-being and health among older households as individuals age. Given the changing context of Medicare, pensions, and Social Security, many demographic, sociological, and health components of aging may be best understood in concert with economic analyses. Recently developed data indicate that Medicare hospital expenditure growth is not restricted to the highest-cost beneficiaries, but occurs across the board. Similar rates of hospital expenditure growth were found among high-cost and low-cost users, and similar growth rates occur among different age, race, and gender groups. Related research has found that more use of intensive procedures, many of which are relatively low cost, has accounted for much of the growth in hospital expenditures for Medicare beneficiaries in recent years. Thus, more characterization of the specific technologies associated with rising expenditures might be particularly useful to guide strategies for cost containment. Research has made significant progress in demonstrating how some provisions of Medicare policy can actually result in relatively more frequent use of certain intensive procedures.

Other work has measured the effectiveness of alternative treatments in improving health outcomes. Results suggest that the use of invasive procedures for heart attack patients could be reduced by at least one-fourth with no consequences for mortality, but with savings of over \$300 million per year in hospital costs alone. Similar studies will be carried out examining heart arrhythmias and major cancers and will include outcomes such as the subsequent development of medical complications.

Intramural Research Program

In addition to the extramural research supported through grant and contract awards, NIA directly funds and conducts aging-related research in its own intramural laboratories located at the Gerontology Research Center in Baltimore, Maryland, as well as on the NIH campus in Bethesda.

Characterization of Normal Aging

In order to understand the biological changes found in various disease states associated with old age, it is important that the changes occurring in normal aging be properly defined. At NIA laboratories, these changes are studied at the systemic, cellular, and molecular levels. One area of study focuses on identifying the mechanisms responsible for the progressive cell loss observed in the aging brain. This work is complemented by longitudinal studies assessing the general decline in total brain mass, the increases in cerebrospinal fluid volumes, and the difference in brain function observed in aging. Using a variety of testing methods, researchers at the NIA have found that blood flow to the brain during information processing differs significantly between healthy young and old subjects. It also has been reported that increasing age is associated with difficulty in shifting attention from one sense (sight, hearing, etc.) to another. These results complement other studies showing immediate visual memory impairment in older participants. One theory regarding the aging process and some age-associated diseases is that such changes occur as a result of accumulated damage to the genes and an inability to repair damage to the genes. Recent studies by scientists at NIA have demonstrated that gene repair declines with increasing age. Ongoing studies are clarifying the mechanisms of genetic repair which may lead to a better understanding of how repair mechanisms are altered by the aging process.

Factors That Alter Normal Aging

In an attempt to improve the longevity and quality of life, scientists seek medical interventions that reduce the degenerative changes associated with aging. At the NIA, several laboratories have been successful in developing new strategies that appear to ameliorate some of the deleterious changes associated with aging. Scientists are examining risks associated with heart disease, estrogen hormone deficiencies, and dietary factors. For example, it is known that reducing caloric intake by about 30 percent lengthens the life span of laboratory rats and that these animals have a lower incidence of cancer and other diseases. Parallel studies are now being done in monkeys. These studies aim to identify the biochemical mechanisms that are altered by caloric restriction. It is hoped that the results from these studies will lead to development of interventions that can promote longevity and reduce age-associated diseases.

Novel Treatment Intervention Strategies

Current treatment for many diseases associated with aging relies on the use of new or improved pharmaceutical compounds. However, other methods are also being explored including the use of gene therapy. Experimental gene therapy is being used to (1) replace damaged or "bad" genes, (2) add new (or previously deleted) genes, or (3) increase or decrease the production of critical proteins. NIA researchers are evaluating the possible roles gene therapy may have for treatment of age-associated diseases such as heart disease, central nervous system degeneration, and cancer. Studies are underway to investigate if gene therapy can be used to enhance blood circulation in animal models of chronic heart disease. Using laboratory rabbits bred for the study of heart disease, NIA scientists have successfully induced the growth of new coronary blood vessels to reestablish blood flow following heart attack. In another study, gene therapy is being tested as a way to combat the renarrowing of blood vessels following angioplasty, a technique used to open narrowed coronary arteries. Gene therapy is also being tested in laboratory animal studies of Parkinson and Huntington diseases. These studies inserted a dopamine (a neurochemical) receptor gene into cells normally deficient in dopamine receptors. The results from these studies were dramatic and showed that the cells with the inserted dopamine receptor gene produce new, normally functioning, dopamine receptors that improved motor control in the animals.

Alzheimer's Disease

Although the exact cause of Alzheimer's disease (AD) is still unknown and therapeutic treatments remain limited, the pace of new discoveries continues to increase. One of the characteristic features of AD is the accumulation of amyloid in brain plaques, a defining pathologic change associated with the disease. NIH researchers have found a possible link between specific mutations in the amyloid precursor protein and the characteristic neuronal cell death that is seen in AD patients. Early detection studies have reported that identifiable cognitive changes are evident in patients who subsequently progress to develop clinically apparent AD. Similarly, specific cognitive changes have been identified with sustained attention and immediate visual memory tasks. Although it is unclear where the cellular and biochemical changes initially occur in the brains of AD patients, there is a consistent decrease in the level of acetylcholine (a key neurotransmitter). Scientists at the NIA are researching new drug therapies for treatment of AD which target this and other neurotransmitter systems. One such candidate agent, phenserine, dramatically improved the ability of laboratory rats that had memory-affecting brain lesions, to navigate a maze. This drug is now in preclinical toxicology testing.

Cancer

NIA researchers are studying cancers that increase in incidence with aging, including breast, prostate, and colon cancers. It is known that through normal cellular processes, oxygen is metabolized and forms several compounds (metabolites) which, if not cleared, appear to be toxic to cells. The accumulation of these metabolites appears to cause

genetic damage that if left unrepaired by the cell, can seriously interfere with its ability to produce key proteins, and may initiate the transformation of a normal to a cancerous cell. One group of NIA researchers is specifically studying the role oxidative damage plays in breast cancer. Another group is studying the genetic programming that is thought to determine how breast cancer cells divide and proliferate. Collectively, these studies will advance our understanding of the genetic changes involved in breast cancer, which may help us understand the cause for other cancers such as colon and prostate.

Diabetes

Diabetes is a common illness among the elderly. It is the high glucose blood levels that lead to most of its clinical complications including blindness, vascular disease, and kidney disease. Adult diabetes is associated with a (1) diminished ability of the pancreatic beta cells to release insulin in response to blood glucose, and (2) reduced sensitivity of target tissues to insulin. Research efforts are directed at developing methods to lower blood glucose safely by restoring glucose sensitivity to beta cells and improving insulin action at the target cells. The NIA's interest in finding new ways to maintain the pancreatic beta-cell function in aged animals has led to the cloning of the genes that control beta-cell regeneration in mice. NIA investigators have also synthesized a new compound that increases insulin receptor signaling when introduced into intact cells. The development of such reagents that act as specific modulators of insulin receptor function may provide an effective way to treat diabetes.

Osteoporosis

Osteoporosis occurs frequently among the elderly, and is associated with increased morbidity and mortality. NIA researchers have discovered that there are several deficits associated with aged bone including reduced bone formation, reduced number of cells which make bone, and impaired production of the compounds needed to make and maintain bone. Researchers are investigating several interventions for treatment of osteoporosis including enzyme regulation, cell replacement, and growth factor supplementation. These scientists have found that anticollagenase (an enzyme) treatment can prevent the bone loss seen in certain laboratory animals used to study osteoporosis. It is hoped that similar studies in patients can be conducted to determine if such an approach will work as a treatment for osteoporosis in humans.

Baltimore Longitudinal Study on Aging

The NIA manages and operates the Baltimore Longitudinal Study on Aging (BLSA) which began in 1958. To date, over 2,200 men and women research volunteers have participated. Recent studies using BLSA participants found that women who received estrogen hormone treatment made significantly fewer errors in short-term visual memory tasks than women not taking estrogen. Even women who had recently started estrogen treatment had less memory loss compared to women who never received estrogen therapy. These findings support a beneficial role of estrogen replacement on cognitive functioning

in aging women. In prostate cancer, BLSA studies have altered the standard of practice. Rather than using an absolute value of serum levels of prostate specific antigen (PSA) to screen for prostate cancer, data from BLSA studies have showed that the rate of change of PSA levels over time is a more specific indicator of disease. Restricting diagnostic biopsies to patients with PSA increases greater than 0.75 units/yr. can significantly reduce the number of biopsy procedures thereby reducing the total number and cost of unnecessary surgeries. Other studies using BLSA participants have provided equally valuable scientific information for other medical conditions including cardiovascular disease, and AD.

Research Management and Support

The research and management support (RMS) activity provides administrative support and scientific management for the extramural grants and contract awards, for NIA's intramural research program, as well as for overall program direction and policy development. The extramural initiatives supported by NIA have been developed and are managed by the extramural program staff funded by the RMS activity. Scientific staff members focus their efforts on developing research initiatives, reviewing, awarding, and administering grants/contracts on aging research and training to universities, hospitals, medical centers, and other organizations. The RMS mechanism also provides funding for facility support costs, related expense items essential to all research programs, and the mandated Alzheimer's Disease Education and Referral (ADEAR) Center which gathers, maintains, and disseminates information on Alzheimer's disease research and services. The center operates a toll-free telephone number to provide the latest information and referral services to health professionals. The NIA has developed a national health education campaign to inform health professionals and the public about the importance of the pneumococcal pneumonia vaccine. Direct support is also provided for the operation of several interagency coordinating committees related to aging research; NIA is chair or co-chair of these committees which include the Federal Forum on Aging, and the DHHS Advisory Panel on Alzheimer's Disease.

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Budget Mechanism

	1995		1996		1997	
	No.	Amount	No.	Estimate	No.	Estimate
Research grants						
Research projects:						
Noncompeting	645	\$193,124,000	647	\$188,877,000	718	\$207,015,000
Admin supplements	(95)	4,131,000	(51)	2,866,000	(51)	2,866,000
Competing						
Renewal	80	24,314,000	95	37,148,000	79	32,059,000
New	162	35,455,000	200	44,520,000	170	38,550,000
Supplemental	13	1,894,000	14	2,170,000	14	2,240,000
Subtotal, competing	255	61,663,000	309	83,838,000	263	72,849,000
Subtotal, research projects	900	258,918,000	956	275,581,000	981	282,730,000
SBIR/STTR						
Subtotal, research projects	41	7,627,000	43	8,222,000	53	10,282,000
	941	266,545,000	999	283,803,000	1034	293,012,000
Research Centers						
Spec/comp centers	63	57,096,000	63	57,620,000	63	57,620,000
Other research						
Research career program	122	10,355,000	119	10,353,000	119	10,353,000
Minority biomedical research		781,000		933,000		933,000
Other research related	22	1,914,000	29	2,103,000	29	2,103,000
Subtotal, other research	144	13,050,000	148	13,389,000	148	13,389,000
Total, research grants	1,148	336,691,000	1,210	354,812,000	1,245	364,021,000

Training						
Individual awards:						
Noncompeting Competing	21	574,000	21	537,000	34	833,000
	22	505,000	25	640,000	12	362,000
Subtotal, individual	43	1,079,000	46	1,177,000	46	1,195,000
Institutional awards:						
Noncompeting Competing	335	9,077,000	360	10,014,000	333	9,406,000
	88	2,401,000	76	2,117,000	103	2,907,000
Subtotal, institutional	423	11,478,000	436	12,131,000	436	12,313,000
Total, training	466	12,557,000	482	13,308,000	482	13,508,000
Research & development contracts						
Intramural Research Research management and support	40	22,253,000	45	22,919,000	45	22,919,000
	FTEs 265	38,220,000	FTEs 260	40,333,000	FTEs 260	40,333,000
	164	22,443,000	160	20,760,000	160	20,760,000
TOTAL	429	432,164,000	420	452,132,000	420	461,541,000
Clinical Trials						
		(12,811,000)		(15,587,000)		(15,292,000)

NOTE: Includes 4 FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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National Institute on Aging

Budget Authority by Activity
(Dollars in thousands)

	1993 Actual FTE Amount	1994 Actual FTE Amount	1995 Actual FTE Amount	1996 Estimate FTE Amount	1997 Estimate FTE Amount	Change FTE Amount
Extramural Research Aging	---	\$358,934	---	\$371,486	---	\$12,552
Intramural	305	38,259	265	38,220	260	40,333
Research Management and Support	167	23,090	164	22,421	160	20,760
Total, obligations	472	398,370	429	432,127	420	461,541
Unobligated balance lapsing	---	18	---	437	---	---
Total, Budget Authority	472	398,378	429	432,164	420	461,541

+9,409

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NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Summary of Changes

1996 Estimated budget authority.....	\$452,132,000
1997 Estimated budget authority.....	461,541,000
Net change.....	+9,409,000

	1996 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
Changes:				
A. <u>Built-in:</u>				
1. Intramural				
a. Within-in grade increases		\$19,209,000		+\$265,000
b. Annualization of January 1996 pay increase		19,209,000		+122,000
c. January 1997 pay raises		19,209,000		+441,000
d. Payment for centrally furnished services		4,911,000		+3,000
e. Increase for service and supply fund		2,918,000		+72,000
f. Increased cost of laboratory materials & other supplies		13,295,000		+325,000
Subtotal				+1,228,000
2. Research Management & Support:				
a. Within-in grade increases		10,145,000		+177,000
b. Annualization of January 1996 pay increase		10,145,000		+64,000
c. January 1997 pay raises		10,145,000		+234,000
d. Federal employees compensation fund, unemployment compensation		10,145,000		+5,000

Summary of Changes--continued

	1996 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
e. Payment for centrally furnished services		2,887,000		+39,000
f. Increase for service and supply fund		1,546,000		+38,000
g. Increased cost of laboratory materials & other supplies		6,182,000		+155,000
Subtotal				+712,000
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	647	191,743,000	+71	+18,138,000
b. Competing	309	83,838,000	-46	-10,989,000
Subtotal	956	275,581,000	+25	+7,149,000
2. SBIR/STTR	43	8,222,000	+10	+2,060,000
Subtotal	999	283,803,000	+35	+9,209,000
3. Research centers	63	57,620,000	0	0
4. Other research	148	13,389,000	0	0
5. Training	482	13,308,000	0	+200,000
6. Contracts	45	22,919,000	0	0
	(FTEs)		(FTEs)	
7. Intramural	260	40,333,000	0	-1,228,000
8. Research Management and Support	160	20,760,000	0	-712,000
Subtotal				+7,469,000
Total Changes				+9,409,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Full-time equivalent employment	420	420	0
Full-time equivalent of overtime and holiday hours	2	2	0
Average SES salary	\$114,478	\$114,478	0
Average GS grade	10.6	10.6	0
Average GS salary	\$39,608	\$40,796	+\$1,188
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207)	\$60,034	\$61,835	+\$1,801
Average salary of ungraded positions	\$35,929	\$37,007	+\$1,078
Personnel compensation:			
Full-time Permanent	\$16,024,000	\$16,959,000	+\$935,000
Other than full-time permanent	4,280,000	4,653,000	+373,000
Other personnel compensation	670,000	670,000	0
Special personnel service payments	3,100,000	3,100,000	0
Total, personnel compensation	24,074,000	25,382,000	+1,308,000
Personnel benefits	5,000,000	5,000,000	0
Benefits for former personnel	280,000	280,000	0
Travel and transportation of persons	525,000	525,000	0
Transportation of things	111,000	111,000	0
Rental payments to GSA	1,000,000	1,000,000	0
Rent, communications, and utilities	4,070,000	4,070,000	0
Printing and reproduction	372,000	372,000	0
Other Services:			
Consulting services	38,000	38,000	0
Other services	5,060,000	4,675,000	-385,000
Purchases from Govt.accts	23,958,000	23,430,000	-528,000
O&M Facilities	730,000	630,000	-100,000
R&D Contracts	9,949,000	9,949,000	0
Medical Care Payments	50,000	50,000	0
O&MEquipment	2,643,000	2,543,000	-100,000
Subtotal, other services	42,428,000	41,315,000	-1,113,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Vaccines	7,000	7,000	0
Supplies and materials	3,679,000	3,484,000	-195,000
Equipment	2,353,000	2,353,000	0
Grants, subsidies, & contributions	368,120,000	377,529,000	+9,409,000
Insurance claims & indemnities	111,000	111,000	0
Interest & dividends	2,000	2,000	0
Total budget authority by object	452,132,000	461,541,000	9,409,000

NOTE: Includes 4 FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

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Administrative Costs

	FY 1996 Estimate	FY 1997 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)	16,024,000	16,959,000	+935,000
Other than Full-time Permanent (11.3)	4,280,000	4,653,000	+373,000
Other Personnel Compensation (11.5)	670,000	670,000	0
Special personnel service payments (11.8)	3,100,000	3,100,000	0
Total Personnel Compensation (11.9)	24,074,000	25,382,000	+1,308,000
Civilian Personnel Benefits (12.1)	5,000,000	5,000,000	0
Benefits to Former Personnel (13.0)	280,000	280,000	0
Travel (21.0)	525,000	525,000	0
Transportation of things (22.0)	111,000	111,000	0
Rental Payments to Others (23.2)	0,000	0,000	0
Communications, Utilities, and Miscellaneous Charges (23.3)	4,070,000	4,070,000	0
Printing and Reproduction (24.0)	372,000	372,000	0
Other services:			
Consulting services (25.1)	38,000	38,000	0
Other services (25.2)	5,060,000	4,675,000	-385,000
Purchases from Govt.accts (25.3)	10,939,000	10,411,000	-528,000
Operation & Maintenance of Facilities (25.4)	730,000	630,000	-100,000
Operation & Maintenance of Equipment (25.7)	2,643,000	2,543,000	-100,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal, other services	19,410,000	18,297,000	-1,113,000
Supplies and materials (26.0)	3,679,000	3,484,000	-195,000
Total	57,521,000	57,521,000	0

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Significant Items in the House and Senate Appropriations Committee Reports1996 House Appropriations Committee Report LanguageItem

Alzheimer's Disease - House Report 104-209, page 71 states: "The Committee is aware that a planning process financed with private foundation support has recently been conducted by the Institute to identify promising strategies to prevent or delay the onset of Alzheimer's disease. This process has identified many promising research opportunities, including prevention of the formation of amyloid and the role of apolipoprotein E in causation of Alzheimer's disease. The Committee encourages the Institute to pursue these research opportunities and to enhance resources targeted to these areas."

Action Taken or to be Taken

A series of planning meetings sponsored by the Fisher Foundation for Alzheimer's Research in conjunction with the NIA identified a number of priorities for NIA-sponsored Alzheimer research. Among them were strong recommendations to pursue genetic research to locate genes such as ApoE4, which place individuals at higher risk to develop the disease. Research performed in several of NIA's Alzheimer's Disease Centers resulted in the discovery of two new genes in 1995 which cause familial Alzheimer's disease. These genes, on Chromosomes 14 and 1, have striking similarities and their identification has opened up entirely new strategies to identify the gene products and their role in cell function. These are only two examples of research opportunities that were identified in the planning meetings that NIA will continue to support.

Item

Cardiovascular Aging Research - House Report 104-209, page 71 states: "The Committee believes that research on cardiovascular aging is important and encourages NIA to maintain its innovative extramural and intramural cardiovascular research programs."

Action Taken or to be Taken

NIA has published a program announcement on "Aging, Vascular Stiffness, and Cardiovascular Function" to further stimulate biomedical research on age-associated, blood vessel stiffening and the importance of stiffening in contributing to the development of cardiovascular disease. NIA convened a cardiovascular aging panel that assisted the Institute in identifying high priority research areas and plans to publish the panel's research recommendations to stimulate innovative

extramurally-supported research on the aging cardiovascular system. Examples of new intramural research in cardiovascular aging include: studies showing that exercise training can improve cardiovascular performance in older persons regardless of one's pretraining fitness level; studies supporting the potential use of gene therapy to improve blood flow in tissues suffering from atherosclerosis; and research testing the feasibility of a novel drug delivery system to reduce the rate of narrowing of blood vessels in coronary heart disease after balloon angioplasty.

Item

Nutrition - House Report 104-209, pages 71/72 state: "....The Committee continues to stress the importance of nutrition research at NIA, including continued research on the role of caloric restriction in reducing the incidence of disease among the aged and research regarding nutrition, frailty and sarcopenia. In addition, the Committee encourages NIA to consider supporting research on nutrition screening and malnutrition and nutrition-related problems among the elderly."

Action Taken or to be Taken

The recent Malnutrition in Older Persons program announcement, together with the NIA's support of more than 100 nutrition-related projects, attests to the high priority status of nutrition research at NIA. The nutrition research supported by the NIA is geared both toward specific diseases, as well as to examining generalized nutritional and metabolic processes during aging, and understanding the role of nutrition in maintaining health for successful aging. The NIA continues to support research projects to study caloric restriction in animal models from mice to non-human primates. NIA is planning a workshop for April 1996 which will bring together scientists, including representatives of the Nutrition Screening Initiative, to focus further attention on an important priority in nutrition research and screening, the development and validation of a nutrition screening instrument.

Item

Demographic Research - House Report 104-209, page 72 states: "Informed policy-making on Federal entitlement programs which support this country's aging population is one of the benefits of the research currently underway at NIA's demographic, behavioral and social research program. The Committee continues to support such research and the analysis of its data, with special emphasis on the Health and Retirement and the AHEAD studies, and similar statistical surveys and data bases."

Action Taken or to be Taken

NIA renewed funding for the Health and Retirement and AHEAD Studies for a further five years and plans to continue to support studies on data needs for an aging population and on modelling the adequacy of retirement income.

1996 Senate Appropriations Committee Report LanguageItem

Task Force on Aging Research - Senate Report 104-145, page 90 states. "....The Committee is particularly pleased to understand what areas of research are of immediate priority and is interested in how the NIA will implement the identified research priorities, including research in basic cognition and neuropsychology; cognitive function through training and environmental support; health behaviors and behavior change over the life course; older drivers; elder-friendly environments; and working into late adulthood. The Committee requests that the Director be prepared to report on NIA's progress in implementing the above priorities during the fiscal year 1997 budget hearings."

Action Taken or to be Taken

The NIA continues to stimulate high quality research in the areas identified as high priority by the Task Force on Aging Research and will be pleased to report on its progress on research priorities specified in the Committee's report.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Authorizing Legislation

	PHS Act Other Citation	U.S. Code Citation	1996 Amt Authorized	1996 Estimate	1997 Amt Authorized	1997 Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Institute on Aging	Title IV, Part C	42§289k-2 289k-5	Indefinite	\$438,824,000	Indefinite	\$448,033,000
National Research Service Awards	Section 487(d)	42§288	Such sums as necessary	13,308,000	Authorization is pending	13,508,000
Total Budget Authority				452,132,000		461,541,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation	1/
1988	156,174,000	203,411,000 2/	199,642,000	194,746,000	
1989	204,770,000	225,578,000	210,222,000	222,643,000	
1990	229,620,000 3/	241,528,000	245,490,000	242,685,000 4/	
1990 Sequester				-3,230,000	
1991	248,938,000	278,311,000 5/	377,733,000	323,752,000 6/	
1991 Sequester				-4,000	
1992	348,558,000	362,528,000	397,176,000	383,382,000 7/	
1993	407,284,000	402,218,000	405,218,000	399,924,000 8/	
1994	394,156,000	420,303,000	420,303,000	420,303,000	
1995 9/ 1995 Rescission	433,701,000	431,198,000	433,198,000	432,698,000 10/ -332,000 11/	
1996	447,608,000	453,917,000	441,072,000 9/	453,917,000	
1997 9/	463,365,000				

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ House Allowance consolidated all AIDS activities in OASH.

3/ The 1990 request excludes funds for the National HIV program (\$870,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Excludes enacted administrative reduction of \$824,000.

5/ Excludes \$9,520,000 in NRSA training programs not considered.

6/ Excludes enacted administrative reductions of \$8,020,000 and \$1,010,000.

7/ Excludes enacted administrative reductions of \$120,000, \$2,783,000, and \$729,000.

8/ Excludes enacted administration reductions of \$3,236,000, \$162,000, and \$1,146,000.

9/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research in FY 1995, in FY 1996 Senate Allowance, and in FY 1997.

10/ Excludes enacted administration reductions of \$233,000, \$2,000, and \$140,000.

11/ Enacted rescission.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Detail of Full-Time Equivalent Employment (FTE)

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Estimate</u>
Office of the Director	80	76	76
Biology of Aging Program	12	12	12
Behavioral and Social Research Program	14	14	14
Geriatrics Program	11	11	11
Neuroscience and Neuropsychology	12	12	12
Office of Extramural Affairs	35	35	35
Epidemiology, Demography, and Biometry Program	17	16	16
Intramural Research Program	<u>248</u>	<u>244</u>	<u>244</u>
	429	420	420

Average GS/GM Grade

1992	10.4
1993	10.3
1994	10.1
1995	10.6
1996	10.6
1997	10.6

NOTE: Includes 4 FTEs associated with HIV/AIDS Research Activities.

Funds to support these FTEs are included in the NIH Office
of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

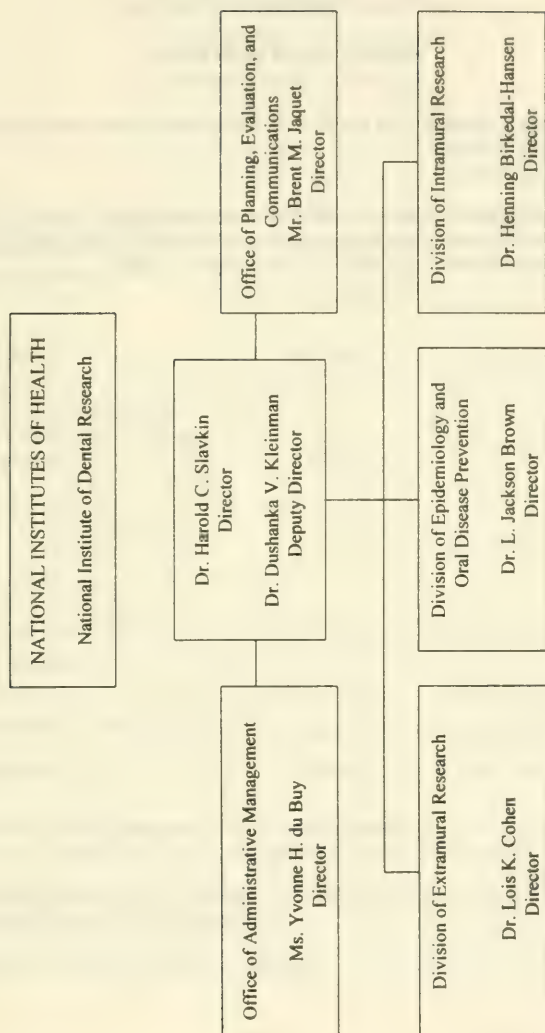
National Institute on Aging

 Program Administration
Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Request
ES-4	5	6	6
ES-2	1	1	1
Subtotal	6	7	7
Total - ES Salary	\$633,900	\$801,346	\$801,346
GS/GM-15	28	28	28
GS/GM-14	35	34	34
GS/GM-13	24	23	23
GS-12	42	41	41
GS-11	49	49	49
GS-10	1	1	1
GS-9	31	30	30
GS-8	12	11	11
GS-7	39	38	38
GS-6	34	33	33
GS-5	10	10	10
GS-4	34	33	33
GS-3	10	10	10
GS-2	1	1	1
Subtotal	350	342	342
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director grade	16	16	16
Senior grade	5	5	5
Subtotal	21	21	21
Ungraded	97	95	95
Total permanent positions	315	315	315
Total positions end of year	474	465	465
Total full-time equivalent(FTE) employment, end of year	429	420	420
Average ES level	3.7	3.7	3.7
Average ES salary	\$105,650	\$114,478	\$114,478
Average GS/GM grade	10.6	10.6	10.6
Average GS/GM salary	\$38,627	\$39,608	\$40,796

JUSTIFICATION OF THE BUDGET ESTIMATES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Institute of Dental Research

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NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to dental diseases, \$174,463,000.

Note—A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

1/

Amounts Available for Obligation

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$162,832,000	\$183,196,000	\$174,463,000
Reduction in accordance with P.L. 103-333.....	(185,000)		
Rescission in accordance with P.L. 104-19.....	(217,000)		
Subtotal, Adjusted Appropriation.....	162,430,000	183,196,000	174,463,000
Real transfer to: Other NIH Institutes through the NIH Director's one-percent transfer authority.....	(139,000)		
Comparative transfer to: Office of AIDS Research, NIH, for HIV activities.....		(12,309,000)	
Comparative transfer from: Other NIH Institutes for Management Fund adjustment.....	821,000		
Subtotal, adjusted budget authority.....	163,112,000	170,887,000	174,463,000
Unobligated balance, lapsing.....	(3,000)		
Total obligations.....	163,109,000	170,887,000	174,463,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1995 -- \$2,827,000; FY 1996 -- \$3,500,000; FY 1997 -- \$3,500,000.

Also excludes funding for HIV activities: FY 1995 -- \$11,733,000; FY 1997 -- \$12,318,000,
included in Office of AIDS Research, NIH.

Note: Excludes \$41,000 in FY 1995 for royalties.

Justification

National Institute of Dental Research

FY 1995		FY 1996		FY 1997		Increase or Decrease	
Actual		Estimate		Estimate			
FTE	BA	FTE	BA	FTE	BA	FTE	BA
314	\$163,112,000	335	\$170,887,000	335	\$174,463,000	---	+\$3,576,000

This document provides justification for the FY 1997 Non-AIDS activities of the National Institute of Dental Research. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The mission of the National Institute of Dental Research (NIDR) is to improve the health of the American people through research focusing on the tissues of the mouth, face and head. Over the years, this research has established that oral health is not only essential to general health, but also that oral, facial and cranial tissues can be used to mirror and model diseases occurring elsewhere in the body. In this way our investigators have become recognized world leaders in the study of tooth and bone biology, disfiguring birth defects, chronic pain conditions, oral cancers, and the oral effects of systemic diseases such as diabetes, osteoporosis, and AIDS. In addition, the Institute supports extensive basic science studies in immunology, microbiology, genetics, behavioral science, materials development, and epidemiology.

Genes of Face--and Body--Value

Molecular biology is now poised to answer one of the most challenging questions in nature: How does a single fertilized egg develop into a human being with head and heart and hands and feet and all the other organs and systems in place and functioning in harmony? Importantly, the answers forthcoming underscore the intimate connection between the face and the rest of the body: The same genes that turn on in the early embryo to regulate the movements of cells destined to become the face, also control the cells fated to become the brain, skin, parts of the heart, the gut, and distant extremities like fingers and toes. All these organs trace their origins to clusters of primordial nerve cells that arch over the primitive spinal column at the back of the embryo to form a "neural crest." Following a precise timetable of development, certain neural crest cells move out to form bulges flanking the sides of the head: the branchial arches. The face develops from the first two branchial arches. Other neural crest cells move to form the curve of the aorta, the great blood vessel that emerges from the heart, while still others migrate to the gut and to the hands and toes. Because birth defects affecting the head are so heartbreaking to behold, so costly to repair, and so common--three-fourths of all congenital malformations seen in newborns affect the head, face or neck--NIDR investigators are committed to understanding what can go wrong in development and what can be done about it.

Now, using the latest techniques of gene mapping and gene cloning, combined with genetic linkage studies of affected families, investigators around the world are discovering developmental genes and pinpointing the causes of a multitude of human birth defects. These include DiGeorge syndrome in which the mouth is small, the nose squared-off and there are defects affecting the aorta and thymus gland, and Treacher-Collins syndrome, in which the ears are deformed, hearing impaired, and the eyes misshapen in a small pointed face. A new gene, "treacle," has just been identified, which, when mutated, causes Treacher-Collins syndrome. NIDR investigators have found the novel developmental gene associated with a form of craniosynostosis, a condition in which the skull bones fuse prematurely, putting pressure on the brain and distorting the shape of the face. Oral scientists have also found the developmental gene for Waardenburg syndrome, which affects eye position and pigmentation so that the eyes are differently colored and the hair may also be variously colored. They have also discovered candidate genes for some forms of cleft lip or palate and congenitally missing teeth.

In some cases the developmental gene at fault is one of the so-called "master" genes, major regulatory genes that orchestrate the behavior of many cell types; in other cases the defect is in a gene coding for a receptor molecule on the surface of a cell, a protein that attracts circulating growth factors that latch on to the receptor and stimulate cells to divide, migrate or differentiate. There are also birth defects associated with the absence of a gene, a situation that scientists duplicate in the laboratory by creating animal "knockouts" with a "null" mutation--in which a specific gene has been eliminated in the embryo.

Our investigators are applying knockout and other experimental methods to study the development of the face and head. "This is really the golden age of human developmental genetics," reported the Director of one of NIDR's Centers for Craniofacial Development in a recent article in *The New York Times*. "Now that we are beginning to identify what genes are involved, we can begin to understand their function -- and how they interplay with one another to form the structure of the face and head." NIDR investigators have already traced the origins of the teeth and jaws to a precise region of neural crest cells in the hindbrain of the embryo. By creating knockout mice missing one or another master gene, they have been able to replicate a number of human developmental defects of oral and facial structures, including one in which there is complete failure of the teeth to develop. Thus the teeth themselves--small, discrete, easy to access and observe--have become sentinel organs in model systems for the study of developmental biology and defects--studies which can be expected to yield new diagnostics and ultimately ways to prevent or correct craniofacial defects using gene replacement therapies.

Teeth as Forensic Evidence

An unexpected finding about a gene vital to the development of tooth enamel is now being exploited commercially in a test kit to determine the sex of a victim of a crime or natural disaster. The kit will aid archaeology research as well, where often only a single tooth may be found at a site. The gene in question governs the production of proteins called amelogenins. The gene is unusual in that it appears on both the female X chromosome and the much smaller male

Y chromosome, but in slightly different forms--sufficient to distinguish the sex of the bearer by DNA sequence analysis.

Mutations in the amelogenin gene and related enamel genes, called enamelines, located on chromosome 1, are associated with the hereditary disorder, amelogenesis imperfecta, in which tooth enamel is either soft, deformed, very thin, or non-existent. As a consequence, the teeth are abnormally discolored and extremely painful: Lacking the protection of their hard enamel surface, the teeth become extraordinarily sensitive to heat and cold, to acids and spices, and other normally neutral stimuli. Children affected suffer psychological problems because of their appearance and may well require dentures in childhood to replace their abnormally weak teeth. Knowledge of the normal and abnormal genes, their protein products and how they function in forming hard tissues (biomineralization) can soon be utilized to develop a new generation of dental materials: restoring teeth nature's way rather than with the 200 million plastic or metal fillings currently placed in the teeth of Americans every year.

Bone Biology and Clinical Studies

Bone and joint diseases affect Americans across the life span, but with the aging of the population and the swelling of the ranks of middle age by the baby boomer generation, the toll taken by osteoporosis, arthritis, Paget's disease and other degenerative diseases of bones and joints can only increase. As one NIDR scientist has said, "It's as though we are outliving our skeletons." Certainly the loss of estrogen is an important factor in the development of osteoporosis in post-menopausal women. Other basic science studies indicate that bone, a dynamic tissue that is constantly being formed and resorbed, undergoes age-related changes in which the forces that lead to resorption gradually surpass our ability to make new bone. These facts of aging life have given impetus to expand research on bone diseases, research that is gaining enormously from basic molecular and cell biology studies of how bone is formed. In these efforts NIDR scientists have discovered whole families of molecules--bone morphogenetic proteins (BMPs) and cartilage-derived morphogenetic proteins (CDMPs) that are essential to bone- and cartilage-building processes. Moreover, they have linked mutations in the genes governing the production of these proteins to specific diseases of bone and cartilage. Most recently, an NIDR scientist has associated a mutation of a member of the CDMP family, CDMP-1, to a form of chondrodysplasia (dwarfism) characterized by a foreshortening that affects the forearms and fingers, the lower legs and toes. The budget request includes provision for a \$1 million enhancement for the NIDR bone research program in FY 1997.

To expand the capability of the NIH Clinical Center to study bone and related diseases in patient volunteers, NIDR has initiated the first protocol in a new Bone Clinic. This study involves extracting certain primordial cells, termed marrow stromal fibroblasts, (MSF) from human bone marrow. These cells give rise to a number of cell lineages including osteoblasts--the cells that produce new bone. The investigators have demonstrated that when such MSF cells were reimplanted in immunosuppressed mice they formed new bone. The next step will be to test the effectiveness of this approach as a way of building up the jaw bone in patients whose bone has become thin because of the loss of teeth.

NIDR has invited all NIH components with an interest in bone research (e.g., the National Institute of Arthritis, Musculoskeletal and Skin Diseases, the National Institute on Aging and the National Institute of Diabetes, Digestive and Kidney Diseases) to collaborate in research studies as well as in the development of the Bone Clinic. Not only can the Clinic advance clinical understanding and treatment for a range of bone and joint conditions, but it can also provide a research training resource for rheumatologists, orthopedists, dentists and other health professionals interested in pursuing careers in clinical research on bone. Collaborations already under way include a study of McCune-Albright's fibrodysplasia, a painful, crippling disease in which there are bone lesions, changes in skin pigmentation, and precocious puberty. NIDR scientists are working with investigators from the National Institute of Child Health and Human Development and the National Institute of Diabetes, Digestive and Kidney Diseases in characterizing the pathology of affected cells. So far it appears that there is a mutation in a key protein in the cell membrane that is involved in signalling the cell to perform certain activities. NIDR has also initiated a Hard Tissues Disorders Group to bring together interested staff scientists for discussions and seminars.

Escalating a War on Oral Cancer

Cancers of the oral cavity and pharynx kill 9,000 people in America every year--more than cervical cancer, malignant melanoma, or Hodgkin's disease. The overall five-year survival rate for all races and both sexes is only 53 percent; it is an abysmal 31 percent for black males, the race and gender group most affected. When oral cancer is not lethal it leaves its stamp in the form of disfiguring surgery, pain, dry mouth (from radiation damage to the salivary glands) and often nerve dysfunction that may affect speech, chewing, and swallowing or blunt taste and other sensory qualities. The combined use of alcohol and tobacco has long been implicated as the major risk factors for oral cancer, but as with other cancers, it takes a number of factors working in concert to transform a normal to a cancerous cell.

These factors are responsible for mutations in the genes of the cell that lead to unchecked cell proliferation and ultimately allow the cell to invade the bloodstream to reach other organs. Thus all cancers are genetic in origin and the excitement of research in recent years lies in the discovery of specific genes called "tumor suppressor genes" that are key players in the control of cell growth and repair. Normally these genes lie on chromosomes that are paired in the cell nucleus, so that there are two copies of each tumor suppressor gene present, one from the mother and the other from the father. If one gene is mutated or missing at birth, the individual is predisposed to develop a particular form of cancer. Over a lifetime, pairs of suppressor genes that were normal at birth may suffer successive "hits" that cause mutations in a kind of two-strikes-and-you're-out game.

Armed with this information as well as studies that have advanced understanding of the changes occurring at each stage of malignant transformation, NIDR has mounted a concerted attack on oral cancers by issuing a request for applications for Oral Cancer Research Centers. This is an invitation to engage teams of basic and clinical researchers in efforts to prevent oral cancer as well as to advance diagnostics and develop better treatments, particularly ones aimed at reversing the cancerous process and restoring cells to normalcy. Such approaches can exploit a

variety of genetic engineering techniques, such as inserting a "suicide" gene into a tumor to cause the cells to self-destruct or replacing the defective gene with the normal form. Another approach pursued by an NIDR investigator is based on re-designing enzymes present in the cell to kill a particular virus--human papilloma virus--thought to be an important co-factor in triggering cancerous changes in oral cells. NIDR and the National Cancer Institute intend to co-fund four Oral Cancer Research Centers in FY 1996.

Chronic Pain Workshops

In December 1995 NIDR, in collaboration with eight other Institutes at the NIH, the Office of Research on Women's Health and the Agency for Health Care Policy and Research, held a workshop to explore what is known about the nature, the prevalence and costs of a selected group of chronic pain conditions ranging from highly prevalent low back pain to relatively rare but extremely painful conditions such as reflex sympathetic dystrophy and post-stroke pain. Participants included leading experts in epidemiology and clinical research who spoke before an audience that included representatives from patient support groups and other interested individuals and organizations. The best data available pertain to low back pain, the most common of the conditions studied, and, in part because more people are affected, the most costly, with estimates on the order of \$80 billion a year in direct and indirect costs (lost wages, etc.). A report summarizing the data available will be supplied to Congress later this year.

The workshop included a discussion of temporomandibular (jaw) disorders which will be the subject of an NIH Technology Assessment Conference to be held this spring. The Conference will focus specifically on management and treatment of these disorders.

The NIDR will expand its efforts in pain and neurosciences research with a \$1 million enhancement in the FY 1997 request.

Regional Research Centers for Minority Oral Health

In 1992 NIDR awarded three-year planning grants for Regional Research Centers for Minority Oral Health. This initiative was dual purpose: to increase research on oral health problems prevalent in racial and ethnic minorities and to enhance the research capability of dental schools whose students are predominantly drawn from racial or ethnic minorities or which serve such communities. The idea was to form consortia linking the minority school with a school with a well-established research track record to promote fruitful exchanges and collaborations. The National Center for Research Resources collaborated with NIDR in providing funds for faculty development activities through the Research Centers in Minority Institutions program. The planning grants were considered Phase I of a program that would lead NIDR to the issuance of a request for applications for Phase II grants--regular five-year center (P50) awards in FY 1995. Four schools successfully competed for the Phase II awards: University of Medicine and Dentistry of New Jersey in collaboration with the University of Connecticut; UCLA School of Dentistry with Charles Drew Memorial University; Meharry Medical College with the University of Alabama at Birmingham School of Dentistry; and New York University College of Dentistry with Forsyth Dental center.

Research planned at the four centers includes:

- ◆ Prevention of infant caries in families enrolled in WIC programs.
- ◆ Physical, economic and psychosocial effects of orofacial injuries.
- ◆ The role of certain tumor suppressor genes, chemical carcinogens and ethanol in oral cancer.
- ◆ Regulation of collagen expression and cell growth in abnormal scarring (keloid formation) seen in African-Americans.
- ◆ Epidemiological description of the oral health status of principal minority groups living in the New York City area.
- ◆ Oral manifestations of pediatric HIV.
- ◆ Risk assessment of destructive periodontal diseases in minority populations.
- ◆ Study of the potential negative impact on the willingness of African-Americans to participate in clinical research protocols based on the legacy of the Tuskegee syphilis study.

Two schools, Meharry Medical College and Charles Drew Memorial University, have applied for and received faculty development awards through the RCMI program.

Twin Studies of Disease Susceptibility

Why are some members in the same family prone to tooth decay or periodontal disease while others seem impervious? Such questions are often cast in terms of the relative influences of heredity vs environment--nature vs nurture. Ideally, scientists look for answers in studies of identical twins (same genes) but exposed to different environments. Now oral scientists have devised their own version of twin studies in a novel approach to susceptibility to adult periodontal disease. They took samples of gingival (gum) connective tissue cells--fibroblasts--from both monozygotic (identical) and dizygotic (fraternal) twins (who are no more or less alike genetically than any siblings in the same family). The investigators exposed the cells to two species of bacteria considered the major culprits in periodontal disease. They observed that both species of bacteria exerted marked negative effects on fibroblast activity and structure. What was noteworthy was that the cells from identical twins responded alike--if the sample from one twin showed conspicuous damage from bacterial exposure, so did the other. In contrast, the cells from fraternal twins showed no similarity. The challenge now is to uncover the molecular mechanisms governing these responses and develop interventions targeted to high-risk individuals to forestall the development of chronic periodontitis and potential tooth loss.

Children's Oral Health: Good News and Bad

NIDR epidemiologists are completing initial analyses of the oral component of the third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994 by the National Center for Health Statistics. Data from physical examinations and responses to questions on dietary habits are being tabulated for 40,000 adults and children across the country.

The new survey will provide an overall profile of the health and eating habits of Americans and can be compared with results from previous surveys to note trends. In examining the oral data NIDR analysts report good news: Declines in tooth decay (dental caries) in children are continuing. Unfortunately, these declines are not evenly distributed. Some 80 percent of the remaining caries is concentrated in 25 percent of American children. The demographic data continue to be analyzed, but findings so far indicate that for children with caries, Mexican-American and non-Hispanic black subgroups had higher percentages of untreated disease than non-Hispanic white children, suggesting that access to care is a problem.

In fall 1996 NIDR will launch its own national epidemiological survey of children's oral health which will provide more detailed data for a sample size large enough to allow year-by-year data analysis for ages 5 through 18. In addition to dental caries, oral health status with regard to periodontal diseases, oral ulcers and other soft tissue lesions will be noted, along with demographic and behavioral data such as cigarette smoking and the use of spit tobacco. Findings from past NIDR surveys have established that early onset periodontal disease, a particularly severe form of disease that can result in early loss of all the teeth, is more prevalent in African-American youths, males in particular. Follow-up studies have since been employed to study affected teenagers and their siblings to search for risk factors, including genetic susceptibility.

Overall Budget Policy

The FY 1997 budget request for NIDR is \$174,463,000, an increase of \$3,576,000 or 2.1 percent over the comparable FY 1996 level of \$170,887,000.

In the FY 1997 President's Budget Request, NIDR's support for research project grants (RPGs) would increase by 4 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 138 competing RPGs, an increase of 18 competing RPGs over FY 1996, and 469 total RPGs, an increase of 3 total RPGs over FY 1996.

A total of 29 research centers will be supported at a cost of \$21,438,000 in FY 1997, the same as in FY 1996.

The other research grant category will be supported in FY 1997 at a total of \$8,382,000 for 113 awards. The Institute will fund approximately 105 research career positions at \$7,405,000; the Minority Biomedical Research Support Program will receive \$70,000; and \$907,000 will be available for other research related awards such as conference grants and scientific evaluation grants.

A total of \$7,101,000 will support approximately 220 full-time training positions (FTTPs) in the National Research Service Awards program in FY 1997, compared to \$6,677,000 for 212 FTTPs in FY 1996. The average cost per trainee is increased by 2.5 percent, including a stipend increase of 2.2 percent.

Research and development contracts will be supported at \$6,690,000, compared to \$6,934,000, a decrease of \$244,000 from FY 1996.

Support for intramural research, including the Institute's Division of Epidemiology and Oral Disease Prevention, will be \$32,207,000, which is the same as FY 1996. Research management and support activities will be funded at \$9,581,000, also the same as FY 1996.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects:						
Noncompeting.....	350	\$54,885,000	329	\$60,922,000	311	\$59,967,000
Administrative supplementals.....	(30)	1,037,000	(30)	1,083,000	(30)	1,114,000
Competing:						
Renewal.....	43	10,646,000	39	10,043,000	45	11,780,000
New.....	88	11,333,000	81	10,756,000	93	12,616,000
Supplemental.....	1	69,000	--	--	--	--
Subtotal, competing.....	132	22,048,000	120	20,799,000	138	24,396,000
SBIR/STTR.....	21	2,781,000	17	2,864,000	20	3,587,000
Subtotal, research projects.....	503	80,751,000	466	85,668,000	469	89,064,000
Research Centers:						
Specialized/comprehensive centers...	29	21,201,000	29	21,438,000	29	21,438,000
Other Research:						
Research career programs.....	104	7,120,000	105	7,405,000	105	7,405,000
Minority biomedical support.....		68,000		70,000		70,000
Other research.....	11	1,295,000	8	907,000	8	907,000
Subtotal, other research.....	115	8,483,000	113	8,382,000	113	8,382,000
Total, research grants.....	647	110,435,000	608	115,488,000	611	118,884,000

Research Training:				
Individual awards:				
Noncompeting.....	10	302,000	21	636,000
Competing.....	11	316,000	--	--
Subtotal, individual.....	21	618,000	21	636,000
Institutional awards:				
Noncompeting.....	145	4,478,000	153	4,833,000
Competing.....	42	1,269,000	38	1,208,000
Subtotal, institutional.....	187	5,747,000	191	6,041,000
Total, research training.....	208	6,365,000	212	6,677,000
Research and development contracts.				
Intramural research.....	235	31,022,000	245	32,207,000
Research management and support....	79	10,266,000	90	9,581,000
Total.....	314	163,112,000	335	170,887,000
Clinical trials.....		(5,035,000)		(5,694,000)

NOTE: Includes 15 FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTEs	Actual Amount	FTEs	Actual Amount	FTEs	Actual Amount	FTEs	Estimate Amount	FTEs	Estimate Amount	FTEs	Amount
Extramural Research:												
Oral diseases and disorders research		\$113,553		\$117,681		\$121,824		\$129,099		\$132,675		\$3,576
Intramural research.	274	29,180	257	30,590	235	30,201	245	32,207	245	32,207	--	--
Research management and support.....	88	10,008	85	9,860	79	10,266	90	9,581	90	9,581	--	--
Total obligations.	362	152,741	342	158,131	314	162,291	335	170,887	335	174,463	--	3,576
Unobligated balance lapsing.....	--	26	--	30	--	3	--	--	--	--	--	--
Total, Budget Authority	362	152,767	342	158,161	314	162,294	335	170,887	335	174,463	--	3,576

NOTE: Includes 15 FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Summary of Changes

1996 Estimated budget authority.....	\$170,887,000
1997 Estimated budget authority.....	174,463,000
Net Change.....	+ 3,576,000

<u>Changes:</u>	<u>1996 Current</u>		<u>Change from Base</u>	
	<u>Estimate Base</u>		<u>Budget</u>	
	<u>FTE</u>	<u>Authority</u>	<u>FTE</u>	<u>Authority</u>
A. Built-in:				
1. Intramural:				
a. Annualization of January				
1996 pay increase.....	--	\$16,111,000	--	+\$102,000
b. Within grade increases.....	--	16,111,000	--	+ 194,000
c. January 1997 pay increase.....	--	16,111,000	--	+ 362,000
d. Unemployment compensation....	--	13,000	--	+ 1,000
e. Payment for centrally				
furnished services.....	--	6,460,000	--	- 131,000
f. Service and Supply fund.....	--	2,826,000	--	+ 126,000
g. Increased cost of laboratory				
supplies, materials and				
other expenses.....	--	6,810,000	--	+ 83,000
Subtotal.....				+ 737,000
2. Research Management & Support:				
a. Annualization of January				
1996 pay increase.....	--	5,230,000	--	+ 33,000
b. Within grade increases.....	--	5,230,000	--	+ 78,000
c. January 1997 pay increase.....	--	5,230,000	--	+ 118,000
d. FECEF/Unemployment				
compensation.....	--	80,000	--	+ 3,000
e. Payment for centrally				
furnished services.....	--	2,260,000	--	- 64,000
f. Service and Supply fund.....	--	1,001,000	--	+ 11,000
g. Increased cost of laboratory				
supplies, materials and				
other expenses.....	--	1,091,000	--	+ 35,000
Subtotal.....				+ 214,000

Summary of Changes -- Continued

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.....	329	\$62,005,000	-18	-\$924,000
b. Competing.....	120	20,799,000	+18	+3,597,000
c. SBIR/STTR.....	17	2,864,000	+3	+723,000
Total.....	466	85,668,000	+3	+3,396,000
2. Research centers.....	29	21,438,000	--	---
3. Other research.....	113	8,382,000	--	---
4. Research Training.....	212	6,677,000	+8	+424,000
5. R&D contracts.....	23	6,934,000	-2	-244,000
	<u>FTE</u>			
6. Intramural research.....	245	32,207,000	--	-737,000
7. Research management & suppo	90	9,581,000	--	-214,000
Subtotal.....				+2,625,000
Total changes.....				+3,576,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Authority by Object

	<u>1996</u> <u>Estimate</u>	<u>1997</u> <u>Estimate</u>	<u>Increase</u> <u>or</u> <u>Decrease</u>
Total compensable workyears:			
Full-time equivalent employment ceiling.....	335	335	---
Full-time equivalent of overtime and holiday hours.....	3	3	---
Average ES salary.....	\$109,000	\$112,000	+\$3,000
Average GM/GS grade.....	10	10	---
Average GM/GS salary.....	\$45,600	\$47,000	+\$1,400
Average salary, grades est. by act of July 1, 1944 (42 USC 207).....	77,800	80,000	+2,200
Average salary of ungraded positions.....	25,600	26,400	+800
Personnel compensation:			
Full-time permanent.....	\$11,800,000	\$12,270,000	+\$470,000
Other than full-time permanent.....	3,292,000	3,427,000	+135,000
Other personnel services.....	411,000	428,000	+17,000
Special personnel services.....	<u>2,317,000</u>	<u>2,411,000</u>	<u>+94,000</u>
Total personnel compensation.....	17,820,000	18,536,000	+716,000
Personnel benefits.....	3,508,000	3,648,000	+140,000
Benefits to former personnel.....	13,000	14,000	+1,000
Travel and transportation of persons	358,000	341,000	-17,000
Transportation of things.....	91,000	86,000	-5,000

	1996 <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Rent, communications and utilities.....	\$767,000	\$784,000	+17,000
Printing and reproduction.....	195,000	184,000	-11,000
Other services:			
Consultant services.....	284,000	270,000	-14,000
Other services.....	381,000	359,000	-22,000
Purchases from Govt. Accounts.....	12,881,000	12,250,000	-631,000
Operation & Maint. of Facil.....	769,000	787,000	+18,000
R&D contracts.....	6,097,000	5,890,000	-207,000
Operation & Maint. of Equip.....	445,000	455,000	+10,000
Supplies and materials.....	3,548,000	3,380,000	-168,000
Equipment.....	1,485,000	1,414,000	-71,000
Grants, subsidies & contributions.....	22,165,000	125,985,000	+3,820,000
Insurance claims and indemnities.....	80,000	80,000	---
Total, budget authority by object.....	170,887,000	174,463,000	+3,576,000

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health

National Institute of Dental Research

Administrative Costs

	1996 Current <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Personnel Compensation:			
Full-Time Permanent (11.1)...	\$11,800,000	\$12,270,000	+\$470,000
Other Than Full-Time Permanent (11.3).....	3,292,000	3,427,000	+135,000
Other Personnel Compensation (11.5).....	411,000	428,000	+17,000
Special Personnel Service Payments (11.8).....	<u>2,317,000</u>	<u>2,411,000</u>	<u>+94,000</u>
Total Personnel Compensation (11.9).....	17,820,000	18,536,000	+716,000
Civilian Personnel Benefits (12.1).....	3,508,000	3,648,000	+140,000
Benefits to Former Personnel (13.0).....	13,000	14,000	+1,000
Travel (21.0).....	358,000	341,000	-17,000
Transportation of Things (22.0).....	91,000	86,000	-5,000
Communications, Utilities, & Miscellaneous Charges (23.3)	767,000	784,000	+17,000
Printing and Reproduction (24.0).....	195,000	184,000	-11,000
Consulting Services (25.1).....	284,000	270,000	-14,000
Other Services (25.2).....	381,000	359,000	-22,000

Administrative Costs- Continued

	1996 Current <u>Estimate</u>	1997 <u>Estimate</u>	Increase or <u>Decrease</u>
Purchases From Government Accounts (25.3).....	12,044,000	11,450,000	-594,000
Operation and Maintenance of Facilities (25.4).....	769,000	787,000	+18,000
Operation and Maintenance of Equipment (25.7).....	445,000	455,000	+10,000
Supplies and Materials (26.0)..	<u>3,548,000</u>	<u>3,380,000</u>	<u>-168,000</u>
TOTAL.....	40,223,000	40,294,000	+71,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1996 Amount Authorized	1996 Appropriation	1997 Amount Authorized	1997 Budget Request
Research and Investigation.....	Section 301	42§241	Indefinite-		Indefinite-	
				\$164,210,000		\$167,362,000
National Institute of Dental Research...	Title IV, Part C, Section 453	42§285	Such sums as necessary		Authorization is pending	
National Research Service Awards.....	Section 487(d)	42§288	Such sums as necessary	6,677,000	Authorization is pending	7,101,000
Total Budget Authority				170,887,000		174,463,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation 1/</u>
1988	\$113,602,000	\$129,106,000 2/	\$131,559,000	\$126,297,000
1989	127,157,000 3/	127,315,000 4/	132,578,000	130,752,000
1990	131,527,000 5/	138,053,000	137,096,000	137,646,000
1990 Sequester				-1,897,000
1991	140,520,000	149,592,000 6/	151,057,000	148,918,000 7/
1991 Sequester				-2,000
1992	160,939,000	161,235,000	158,266,000	158,417,000 8/
1993	166,742,000	161,636,000	163,269,000	161,301,000 9/
1994	163,009,000	169,520,000	169,520,000	169,520,000
1995 10/	163,776,000	162,832,000	162,832,000	162,430,000 11/
1996	168,341,000 10/	183,196,000	165,623,000 10/	183,196,000
1997	174,463,000 10/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ The request excludes funds for AIDS research and education (\$3,562,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Excludes \$5,368,000 in NRSA training programs not considered.

5/ The request excludes funds for the National HIV Program (\$4,269,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

- 6/ Excludes \$5,893,000 in NRSA training programs not considered.
- 7/ Excludes enacted administrative reductions of \$4,354,000.
- 8/ Excludes enacted administrative reductions of \$1,753,000 and a rescission of \$323,000.
- 9/ Excludes enacted administrative reductions of \$1,968,000.
- 10/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
- 11/ Excludes enacted administrative reduction of \$185,000 and a rescission of \$217,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Detail of Full-time Equivalent Employment (FTE)

	1995 Actual Usage	1996 Ceiling	1997 Estimate
Office of the Director.....	9	10	10
Office of Administrative Management.....	16	18	18
Office of Planning, Evaluation, and Communications.....	20	23	23
Division of Extramural Research..	34	39	39
Division of Epidemiology and Oral Disease Prevention.....	42	44	44
Division of Intramural Research...	<u>193</u>	<u>201</u>	<u>201</u>
Total, NIDR.....	314	335	335

Average GS/GM Grade

1991.....	9.7
1992.....	9.6
1993.....	9.8
1994.....	10.0
1995.....	10.0
1996.....	10.0
1997.....	10.0

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute of Dental Research

Program Administration
Detail of End-of-Year Employment

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Request</u>
SBRS.....	1	1	1
ES-4.....	3	3	3
Total, ES Salary.....	\$321,900	\$327,000	\$336,000
GS/GM-15.....	25	25	25
GS/GM-14.....	32	32	32
GS/GM-13.....	22	22	22
GS-12.....	26	26	26
GS-11.....	24	24	24
GS-10.....	1	1	1
GS-09.....	11	11	11
GS-08.....	10	10	10
GS-07.....	40	40	40
GS-06.....	11	11	11
GS-05.....	12	12	12
GS-04.....	13	13	13
GS-03.....	4	4	4
GS-02.....	3	3	3
GS-01.....	<u>1</u>	<u>1</u>	<u>1</u>
Subtotal.....	235	235	235
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade.....	15	15	15
Senior Grade.....	3	3	3
Full Grade.....	3	3	3
Senior Assistant Grade.....	<u>2</u>	<u>2</u>	<u>2</u>
Subtotal.....	23	23	23
Ungraded.....	74	74	74

Detail of End-of-Year Employment - Continued

	1995 <u>Actual</u>	1996 <u>Estimate</u>	1997 <u>Request</u>
Total permanent positions.....	229	229	229
Total positions, end-of-year.....	336	336	336
Total full-time equivalent (FTE) employment, end-of-year.....	314	335	335
Average ES level.....	ES-4	ES-4	ES-4
Average ES salary.....	\$107,300	\$109,500	\$112,700
Average GS/GM grade.....	10	10	10
Average GS/GM salary.....	\$44,500	\$45,600	\$47,000

JUSTIFICATION OF THE BUDGET ESTIMATES

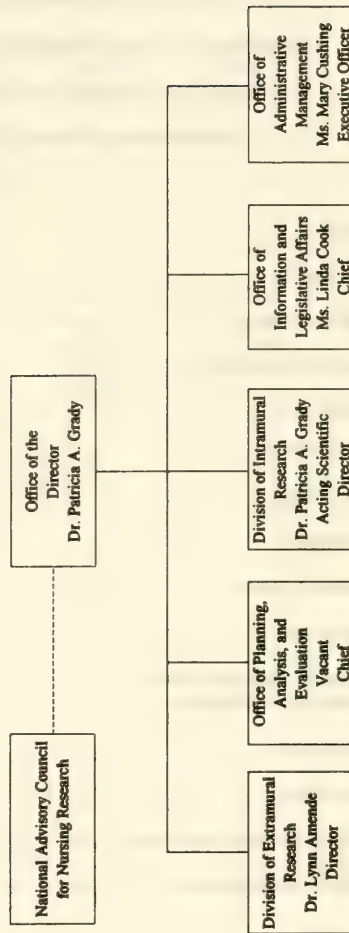
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

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NATIONAL INSTITUTES OF HEALTH
National Institute of Nursing Research
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to nursing research, \$51,951,000.

Note—A regular appropriation for this account had not been enacted at the time this budget was prepared. The 1996 amounts included in this budget are based on the levels provided in the three continuing resolutions: P.L. 104-91, P.L. 104-92 and P.L. 104-99.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Amounts Available for Obligation 1/

	1995 Actual	1996 Estimate	1997 Estimate
Appropriation.....	\$48,237,000	\$55,831,000	\$51,951,000
Reduction in accordance with P.L. 103-333.....	-57,000		
Rescission in accordance with P.L. 104-19.....	-16,000		
Subtotal, Adjusted Appropriation	48,164,000	55,831,000	51,951,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority.....	-41,000		
Comparative transfer to: Office of AIDS Research, NIH for HIV activities.....		-4,896,000	
Comparative transfer from: Other NIH Institutes for Management Fund adjustment.....			
Subtotal, adjusted appropriation.....	48,123,000	50,935,000	51,951,000
Unobligated balance, lapsing.....	-11,000	—	—
Total obligations.....	48,112,000	50,935,000	51,951,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1995 — \$1,975,000; FY 1996 — \$5,550,000; FY 1997 — \$6,550,000.

Also excludes funding for HIV activities: FY 1995 — \$4,577,000; FY 1997 — \$5,015,000,
included in the Office of AIDS Research, NIH.

**National Institute of Nursing Research
Narrative Justification**

Authorizing Legislation - Sections 301 and 487(d) of the Public Health Service Act.
1997 Authorization: Indefinite

Budget Authority:

FY 1995 Actual		FY 1996 Appropriation		FY 1997 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
38	\$48,112,000	44	\$50,935,000	43	\$51,951,000	-1	\$1,016,000

This document provides justification for the FY 1997 Non-AIDS research activities of the National Institute of Nursing Research. Justification of NIH-wide FY 1997 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

The National Institute of Nursing Research (NINR) improves the quality of life for all Americans by promoting healthy lifestyles and behaviors that will ease the effects of disease. Nursing researchers focus on physical and psychological responses to symptoms and treatment of diseases throughout the life span. We all gain humanitarian and economic benefits because of nursing research. Life is improved for the sick and the healthy, while health professionals can care for people more effectively at controlled costs.

The NINR has established a strong science base for nursing research and is a critical part of the biomedical and behavioral research of the National Institutes of Health (NIH). As we begin our second decade at NIH, our research will include additional health care issues. Biochemical and neurological bases of symptoms, as well as side effects of disease and treatment will continue to be emphasized.

The NINR addresses human health across the spectrum of basic, clinical, and behavioral research. We conduct much of this through collaboration with investigators supported by other institutes within the NIH. We have expanded our understanding of many factors that affect health, including those that may delay or suppress the expression of genetic diseases. Traditionally, nursing research scientists have played an instrumental role in improved patient care and delivery of clinical care and NINR continues its support of these important efforts.

The United States is a culturally diverse nation, with different races, genders, ethnic backgrounds and socioeconomic status. Because of this diversity, considering how each disease may affect the various subsets of the population is important. Minority and under served populations experience a higher prevalence of many diseases. To counter this, we are working to make health care more accessible and more affordable for people.

The elderly and people who live in rural and inner city areas are often unable to use mainstream health resources. They may also face socioeconomic barriers to health care, or have other sets of common health issues that nurse researchers can address. Living in rural areas often compounds these health care problems. NINR supported research addresses these issues by checking the health of people participating in community-based health care programs. Our goal is to find program features or practices that promote effective care and improve health.

Nursing research addresses some of the nation's most pressing health problems. Specifically, we emphasize controlling pain and postponing the physical and psychological degeneration associated with Alzheimer's disease and other chronic illness. We seek to understand the interactions among physical environments, individual lifestyles, genetic makeup, and how care givers and patients make health related decisions.

Stories of Discovery

Preserving Personal Independence

Our nation is moving into the 21st century with more Americans joining the ranks of the elderly at a faster pace than ever before. As baby-boomers enter the second half of their lives, they hope to continue to be fully independent, in good health, and actively functioning. However, this is not always possible. Too often, health problems and health care costs spiral out of control, placing extraordinary burdens on patients, care givers and the health care system. Progress must be made through research to postpone and reduce effects of non-fatal chronic illnesses. Sensory impairment, degenerative neurological diseases and musculoskeletal disorders contribute to physical suffering of individuals.

Translating research findings into state-of-the-art nursing interventions is one of NINR's priorities. Nursing care reinforces the belief that older adults can maintain or regain some measure of strength, function, and independence. For example, an elderly woman suffering from a chronic lung disease might lose independence because she is unable to walk even to the corner grocery store. Such situations have been shown to be manageable by providing improved upper body strength training and teaching diaphragmatic breathing exercises.

Research helps us understand the normal aging process and reasons that place elderly Americans at risk for disease and chronic conditions. Nurse researchers promote the functional independence and quality of life of people throughout their lifespan. Unfortunately too many older Americans face the twilight of their life surrounded by the darkness of Alzheimer's disease. It robs their memories, destroys their motor skills, and leaves its victims unable to communicate with their family, friends and health care providers.

Dementia, primarily due to Alzheimer's disease, causes dependency and disability. The disruptive behaviors that occur in the later stages of the disease can devastate families. Often families are left with no other choice but to move their relative from their home into an institution. This loss of personal independence places staggering emotional and financial burdens on patients, their families, and the health care system. NINR has developed effective interventions to slow cognitive decline through mental stimulation exercises and strategies that delay the loss of self-

efficiency. Basic and clinical research projects are essential to continue to find treatments for dementias and other chronic, progressively disabling conditions.

NINR's Intramural Clinical Therapeutics Laboratory (CTL), conducts research related to older Americans. One CTL research program which focuses on urinary incontinence and bacteriuria in the elderly, conducted a recent study of patients with acute hip fracture. The findings showed an increased incidence of postoperative incontinence in men compared with women. This contrasts with the fact that in situations other than hip fracture surgery, urinary incontinence is more common in women than in men. Another study of community-dwelling post-menopausal women is assessing the use of topical estrogen and pelvic muscle exercises to reduce incontinence and associated symptoms. CTL works with scientists in the National Institute on Aging to investigate the relationship between urinary incontinence, bacteriuria, and hypertension to test strategies of controlling these disabling conditions.

Health Knowledge, Attitudes, and Behavior

Habits learned during childhood can help us, or they can come to haunt us as adults. Teenagers have already developed deeply rooted attitudes about alcohol, smoking, nutrition and, physical safety. We need to explore when and how to intervene earlier in a child's life to prevent unhealthy habits from starting. A positive change in behaviors toward physical safety is that while seeing a child wear a bicycle helmet was once unusual, it is now commonplace. We need to continue to promote positive habits and teach people to follow healthy behaviors throughout their lifespans. NINR is also supporting research on ways to change individuals risky health behaviors. One approach tailors intervention programs to match individuals health knowledge and attitudes along with their cultural beliefs.

NINR offers opportunities for researchers to develop and test strategies to reach populations at risk for contracting and spreading infections such as tuberculosis and AIDS. While modern drugs, vaccines, and pesticides are powerful weapons, their use has actually resulted in several drug-resistant viruses and diseases. Lack of public information about prevention and treatment has compounded the problem, resulting in near epidemic proportions of tuberculosis in many cities. Recently a man on a crowded commuter train was found to have active tuberculosis. He exposed many other passengers, placing them at-risk for infection. A number of individuals also continue at great risk for AIDS because they are not motivated to change their behavior or follow medical treatment regimens.

NINR's Research Setting

The NINR supports research at academic sites throughout the United States and in its own laboratories within the NIH program. In 1996 a workshop for an interdisciplinary group of scientists identified opportunities and appropriate roles for NINR within the NIH human genetics research effort. The participants addressed training and career development steps to prepare investigators to conduct these studies. This activity set the stage for collaborative activities in nursing-related genetic research over the next decade.

NINR conducts research related to the responses to specific diseases, such as Alzheimer's disease, AIDS, tuberculosis, cancer, cardiovascular disease, diabetes, and musculoskeletal disorders. Research is also supported on conditions or life cycle events such as pregnancy and the neonatal period. NINR also conducts research on symptoms related to treatment and effects of disease. This approach has both short and long term benefits.

In the short term, focusing on a specific health problem offers the potential of incremental progress, although the application may be limited in scope. In the long term, the development of a comprehensive body of knowledge built on the findings of multiple discrete projects will help create a constellation of measures about management of symptoms common to many health problems. Some of these symptoms include pain, fatigue, cognitive difficulty, muscle wasting, nutritional disturbances, sleep disorders, respiratory distress, urinary incontinence and the effects of major trauma.

Operating as an integral part of the NIH has optimized NINR's ability to set the policy for nursing research and to accomplish the National Nursing Research Agenda. The independence available to the Institute allows for better responses to health issues. Research efforts are also initiated in response to the emerging needs of scientists and practicing health-care professionals. At the same time, NIH provides a stimulating environment to generate many advances in every scientific discipline. As a part of NIH we provide the nursing perspective to scientific advances made by other NIH institutes and aid in development of clinical applications of research.

Through established links with its research constituencies, the NINR can readily work with the scientific community to identify issues arising from new therapeutic approaches to individuals and their families. Moreover, these same networks allow rapid distribution of NINR's research results ranging from scientific exchange among investigators to health care providers using the results.

Benefits and Impact of Research

The NINR will continue to expand and balance the science base to achieve the goals for our broad science areas. The six areas we will concentrate our efforts in 1997 are: cognitive impairment, neurobiology and behavioral science of pain, clinical issues arising from genetic advances, managing treatment side effects, managing chronic wounds, and enhanced physical conditioning for older adults.

Cognitive Impairment: Prevention and Management

Cognitive impairment is a significant public health problem that affects quality of life and health care costs. It is prevalent in all age groups and in many common disorders, such as AIDS-related dementia, stroke, delirium and confusion, Alzheimer's disease, traumatic brain injuries, and non-Alzheimer's type dementia. To prevent and treat this problem, nurses and other health care professionals need additional scientific knowledge on which to base their practice.

The brain has the capacity to change, grow, and recover. Damage, disease, and degeneration associated with biochemical, structural, physiological, and psychological changes may be

modified. A biobehavioral approach is key to understanding and treating cognitive impairment. While researchers know that neurophysiology, cognitive processes, and behaviors are interrelated, they need a keener understanding of the biology of clinical patterns of altered behavior. Research addressing these areas offers the possibility of restoring normal functions of improved cognition, emotion, behavior, health, quality of life, and independent living.

Learning how to modify the structure and function of neural systems to achieve the best therapeutic results is important. An expanded information base of neural systems and human responses associated with altered brain structure and function is needed to properly care for infants, children, and adults with cognitive impairments. This knowledge will serve as the basis for nursing interventions to manage or ease symptoms. Research is needed to address interventions that prevent or delay the onset of intellectual impairment, including cognitive, behavioral, attitudinal, and physical approaches. Pharmacological interventions and non-pharmacological approaches to develop age appropriate behavior in infants and children and manage behavioral, physical and functional problems are also essential. These problems include wandering, falls, sleep disturbances, and maintenance of adequate nutrition that often manifest themselves in health disorders in all age groups. Basic and clinical projects will study neurobehavioral and cognitive effects of dementia, delirium, and confusion, including similarities and differences in these conditions and their assessment and appropriate treatment. Research will assess how to develop supportive interventions to help family caregivers of infants, children, and adults who often experience depressed mood and impaired immune function.

Studies in NINR's Laboratory for the Study of Human Responses to Health and Illness (LHRHI), focus on quality of life and functional status in chronic disease. Investigation into the long-term care burden on the health and well-being of caregivers of elderly men with dementia may lead to interventions that help adaptation and successful coping. This study is conducted with the National Institute on Aging and the National Heart, Lung, and Blood Institute. An LHRHI study has resulted in development of an instrument, the Functional Performance Inventory, useful as a reliable and valid measure of functional performance in chronic illness. This study proved that the actigraph, an easy-to-wear mechanical device that measures activity, is reliable and can distinguish between light, moderate, and heavy activity. Thus, this instrument has the potential for use in studies requiring objective measures of function.

Neurobiology and Behavioral Science of Pain

Pain is a complex phenomenon that can profoundly reduce quality of life. While health research has made many strides in decreasing pain, it still is a critical, common, and a costly health problem both in lost productivity and health care expenses. Substantial progress has been made understanding the neuroanatomical pathways of the sensory systems and the neurophysiological mechanisms involved in pain. Furthermore, understanding the subjective pain experience in individuals presents unique scientific opportunities for basic and clinical research. Even with the same apparent physiology, people react in very different ways to physical events.

NINR is developing measures to relieve pain and sponsors a major research program on the subjective pain experience. Research shows that pain may be life-threatening and can affect the immune and endocrine systems. Sometimes treating pain can cause problems beyond those

arising from the primary condition. Secondary problems include loss of appetite, immobility, and insomnia. To define the neural mechanisms that cause pain we support research at the cellular and molecular levels. By understanding the physical and behavioral mechanisms of pain we hope to find ways to reduce suffering.

It is important to examine pain at the levels of the gene, molecule, cell, organ, and individual. Research is needed on the differences in the pain experience and management due to variables such as genetic differences, endocrine and immune function, stress, psychological status, age, gender, and cultural background. Understanding the neurochemical basis of pain perception and the discovery of targets in the signal transduction pathways as the most effective point for interventions in the control of pain is necessary. Identification of compounds that mimic the effect of endogenous analgesic systems is also needed. Systematic studies are needed of the efficacy of pharmacological and behavioral approaches to the control, management and alleviation of pain.

Pain research is a topic of interest across NIH and thus several institutes have formed the Biobehavioral Pain Subcommittee of the NIH Health and Behavior Coordinating Committee. This group coordinates the active collaboration of nine different institutes who sponsor conferences and publish research initiatives. They will explore the molecular mechanisms of pain modulation and control by such variables as genetic differences, neuroendocrine, and neuroimmune changes. NINR projects will refine neuroimaging algorithms for the study of structural and functional correlates of pain perception. Research will examine pharmacologic and other interventions to prevent pain so the initial establishment of neural pathways for pain does not occur.

Clinical Issues Arising from Genetic Advances

Remarkable progress has been achieved in understanding human genetics in the past year. Advances in scientific knowledge and biotechnology will continue to revolutionize health care and increase the importance of multidisciplinary and collaborative research in nursing, genetics, ethics, and epidemiology. The use of protein and other biochemical markers as indicators of genetic expression may help detect predisposed genetic conditions and monitoring changes in health status before symptoms manifest and require treatment. This technology could permit early interventions to prevent or delay the progression of chronic disease and to improve treatment following onset.

As the field of molecular genetics evolves, diagnosis, testing and treatment of genetic disorders will become common tools in health care practice. Research programs are needed to examine interactions among genetic predispositions, environments, and lifestyles. Risk assessment and behavior modification will become an essential part of health care. This will generate a need to identify these risks and to develop strategies for successful intervention. Research will focus on decision making processes needed as our understanding of genetic factors in the onset of disease becomes a reality.

NINR will support research to help individuals and healthcare providers make decisions about genetic concerns. The decision-making process is complex and formidable. An array of

decisions about genetic issues must be made by individuals and health-care providers alike. The initial decision to undergo or forego testing will lead to a cascade of decisions about treatment, prevention, and disclosure for individuals and families. Health-care providers and patients must understand the physiological, psychological, social, and ethical consequences of these decisions. NINR will support research on factors that influence decision-making and the personal, social, and ethical questions posed by advances in genetic diagnosis and therapy. Multidisciplinary research is needed to address preventing or retarding the progression of disease or its symptoms in genetically predisposed individuals.

NINR's Intramural Clinical Ethic Laboratory (CEL) is a new effort of the Institute to develop a program of research on clinical ethics. The initial research focuses on decision making about participating in genetic studies and clinical trials. The CEL is developing studies to examine the process of, and influences on decisions made by persons with HIV infection about participating in clinical research. Researchers also hope to determine how much and what people know about the intent and process of research.

The CEL program seeks to understand specifically why people participate in studies and the various factors that influence individuals to decide for or against genetic testing. A clearer understanding of the variety of motivations for participation will help us to assess how these reasons combine with the medical intervention to affect the outcome for an individual. Knowledge of the influences and motivations for participation will provide an empirical basis for dialogue on the ethics of human subjects research. This research will also help the process and quality of informed consent and provide direction for additional research initiatives involving human decision processes.

The CEL efforts will help the biomedical research community by providing practical information for recruitment and referral of subjects into clinical research. The research will also help to discover the best ways to recruit subjects to clinical trials while maintaining ethical standards and ensuring efficient achievement of statistical power in a particular project.

Managing Treatment Side Effects

The medical treatment of diseases such as cancer and AIDS often involves a temporary increase in discomfort, disability, and may even involve life-threatening clinical problems. Because of that, some people are almost as afraid of the treatment as they are of the disease. For cancer patients, the side effects of chemotherapy may include nausea and vomiting, hair loss, pain, and depression. Many individuals with conditions such as hypertension, autoimmune disorders, and even infectious diseases choose to stop participating in the full recommended treatment regime. Much of the lack of adherence is a result of the side effects of treatment such as sleep disorders, mood disturbances, anxiety, and altered digestion and bowel patterns. Better understanding and effective management of such responses will increase a person's quality of life.

Helping people find acceptable ways to change their lifestyle to offset the negative responses to treatment increases the likelihood of successful treatment. This also decreases the economic burden of wasted medications and health resources, and reduces the risk of emergence of drug

resistant disease. It is critical that researchers design scientific strategies to increase the frequency with which individuals successfully complete therapy.

NINR's goals include basic and clinical studies to identify the biology of treatment-related symptoms. Support will be given to small studies to develop and test instruments that can assess signs and characteristics of the symptoms and their intensity and duration. Researchers will analyze the patterns of clinical responses to symptoms associated with treatment and assess long-term effects. Studies will address physical, cultural, socioeconomic, educational, and psychological reasons for lack of adherence to treatment regimens.

Managing Chronic Wounds

Chronic wounds are a major national health-care problem, affecting many people at tremendous annual costs. One type of chronic wound is pressure sore development. Factors that contribute to the problem include immobility, advanced age, malnutrition, friction, moisture, blood pressure deviations, and elevated temperature. In patients with spinal cord injuries, pressure sore development has a statistically significant association with malnutrition, alcoholism, and mental disorders. Nurses are largely responsible for educating these individuals about prevention of pressure sores and caring for skin breakdowns. The effect of spinal cord injury on the chronic wound environment is poorly understood. Care of individuals with spinal cord injury and pressure sores requires clinical investigation because both conditions have immediate and long term implications for skin integrity, wound healing capacity, and risk of subsequent chronic wound development.

Understanding the mechanisms of chronic wounds and fostering collaboration on this issue between basic and clinical research scientists has been possible through multi-Institute initiatives on chronic wound healing. This effort includes several NIH components, the National Institute of Arthritis and Musculoskeletal and Skin Disorders, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, the National Institute of Child Health and Human Development and the National Institute of General Medical Sciences.

Research efforts will emphasize managing chronic wounds and preventing pressure sores in victims of spinal cord injury. NINR will continue to collaborate with the National Institute of Arthritis and Musculoskeletal and Skin Disorders, the National Institute on Aging, and other department agencies through the Skin Interagency Committee. In 1997 we will begin studies to define the benchmark of standard care for treatment of venous stasis ulcers, diabetic ulcers, and pressure sores and use this as the base for clinical trials.

NINR research examines the cellular and biochemical features of wound fluid and tissue samples collected from pressure sores of patients with spinal cord injuries. In this research we will examine the compounds that destroy proteins (proteases) or that block destruction of proteins (protease inhibitors) involved in maintaining intact skin. Tests are conducted for the presence and absence of serum and tissue protease inhibitors. Tissue sections are examined for expression of plasminogen activators. Scar formation at the healing site is assayed for the distribution of fibronectin and collagen, two proteins significant to the healing process. These biochemical and

cellular studies identify the fundamental biological processes that result in chronic wounds and will yield information needed for effective treatment and prevention of wounds.

Enhanced Physical Conditioning for Older Adults

Many older adults lack mobility, strength, balance, and endurance. This raises physical problems and can cause the loss of independent living and increase the risk of injury. Survey data suggest that 20-40 percent of Americans age 75 and older cannot climb ten stairs, walk one-quarter mile, or lift ten pounds. It is well known that individuals who take part in physical activity, conditioning, and exercise generally gain positive health benefits. These benefits have no age limitations. However, despite all the evidence about positive aspects of remaining active, 70 percent of older adults do not have a regular exercise program, and 60 percent say they have not walked a mile in the past year.

A central issue in the care of older adults is to maintain and promote physical and functional health required for independent, active, daily living. This effort builds on the 1990 initiative on "Reducing Frailty and Injuries in Older Persons" cosponsored by NINR and the National Institute on Aging. These cooperative field studies focused on the development and testing of biomedical, behavioral, or environmental interventions to reduce the loss of functional capacities and to prevent fall-related injuries in older adults.

The long-term goal of this initiative is to stimulate further research on the efficacy and effectiveness of physical activity, conditioning, and exercise in improving the health status of older adults. To achieve this goal, researchers will explore the impact of gender and social relationships beyond the direct family in the participation in physical activity, conditioning, and exercise regimens. Researchers will also design and test interventions with larger samples and greater participation rates to improve the validity of findings related to mobility, strength, and balance. Another goal is to understand health behaviors and environmental conditions that foster activities leading to improved strength, basal metabolic rate, balance, endurance, and aerobic capacity.

NINR Budget Policy

In the FY 1997 President's Budget Request, NINR support for research project grants (RPGs) would increase 2.8 percent over FY 1996. NIH plans to revise average cost increases identified in the Financial Management Plan to reflect declining inflation rates. For FY 1997, inflation is projected to have declined to 2.2 percent for the Gross Domestic Product and 3.7 percent for the Biomedical Research and Development Price Index. Thus, in FY 1997, noncompeting RPGs would receive direct cost increases over FY 1996 awards of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These levels will maintain stability of support within the extramural grantee community while providing new research opportunities.

The 1997 budget request for the NINR is \$51,951,000 and 43 FTEs. This amount represents an increase of \$1,016,000 or approximately 2 percent over the 1996 level. Within this budget, the request for research project grants is \$38,061,000.

This level will support 151 research project grants, one less than supported in 1996. Of these grants, 92 will be awarded as noncompeting and 55 will be competitively awarded. Four additional projects will be awarded under the Small Business Innovative Research and Small Business Technology Transfer (SBIR/STTP) program. Research training grants will include stipend increases of 2.2 percent and efforts will be made to increase the proportion on postdoctoral trainees within the total pool of trainees.

The 1997 budget request for Intramural Research is \$644,000, the same amount budgeted for 1996. This budget supports intramural laboratory research in the topics of clinical therapeutics, human responses to health and illness, and clinical ethics.

The 1997 budget request for Research Management and Support is \$4,309,000, the same amount budgeted for 1996. The Research Management and Support (RMS) activity supports the extramural scientific and internal administrative staff for the Institute. The predominant activity in RMS is staffing the Division of Extramural Programs to ensure direction, review, and management for the Institute's grants and training scientific portfolio. The RMS activity provides managerial and administrative services for leadership of the NINR, planning and evaluation, and financial and personnel administration for the Institute.

The NINR has scrutinized its administrative operations during the last year. Several program structures have been flattened, reducing the number of supervisors. In addition, work processes are examined to discover steps that can be simplified or eliminated. Additional effort is made to collaborate with other bodies throughout NIH to ensure that NINR exploits all existing management resources available. Efforts will continue to carefully examine and streamline work processes and procedures wherever possible to reduce costs and improve efficiency in conjunction with the Administration's efforts to reinvent Government.

NATIONAL INSTITUTES OF HEALTH
National Institute of Nursing Research
Budget Mechanism

	1995 Actual		1996 Estimate		1997 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting.....	102	\$23,110,000	104	\$25,356,000	92	\$23,614,000
Administrative supplements.....	(11)	301,000	(15)	432,000	(15)	432,000
Competing:						
Renewal.....	6	1,530,000	6	1,436,000	7	1,700,000
New.....	42	9,364,000	38	8,821,000	48	11,317,000
Supplements.....	0	0	0	0	0	0
Subtotal, competing.....	48	10,914,000	44	10,259,000	55	13,017,000
SBIR/STTR.....	9	912,000	4	998,000	4	896,000
Subtotal, research projects.....	159	35,237,000	152	37,045,000	151	38,061,000
Research Centers.....	6	1,766,000	6	1,873,000	6	1,873,000
Other research:						
Research career programs.....	14	1,055,000	14	1,284,000	14	1,284,000
Coop. Clin.....		150,000		158,000		158,000
Other research related.....	2	232,000	8	516,000	8	516,000
Subtotal, other research.....	16	1,437,000	22	1,958,000	22	1,958,000
Total, research grants.....	181	38,440,000	180	40,876,000	179	41,892,000

Training:					
Individual awards:					
Noncompeting.....	47	683,000	77	1,224,000	78
Competing.....	18	272,000	29	486,000	29
Subtotal, individual.....	65	955,000	106	1,712,000	107
Institutional awards:					
Noncompeting.....	85	2,378,000	81	2,034,000	78
Competing.....	23	589,000	22	512,000	21
Subtotal, institutional.....	108	2,977,000	103	2,546,000	97
Total, training.....	173	3,932,000	209	4,258,000	204
Research and development contracts:					
.....	1	457,000	3	848,000	3
Intramural.....					
.....	8	613,000	8	644,000	8
Research management and support.....					
.....	36	4,681,000	41	4,309,000	41
Total.....	44	46,123,000	49	50,935,000	49
NOTE: Includes FTE's associated with HIV Research Activities. Funds to support these FTE's are included in the NIH Office of AIDS Research.					
51,951,000					

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Authority by Activity
(Dollars in thousands)

	1993		1994		1995		1996		1997		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Nursing Research.....	—	\$40,476	—	\$41,527	—	\$42,829	—	\$45,982	—	\$46,998	—	+\$1,016
Intramural Research.....	9	373	9	630	8	604	8	644	8	644	0	0
Research management and support.....	43	4,662	44	4,816	36	4,679	41	4,309	41	4,309	0	0
Subtotal, obligations.....	52	45,511	53	46,773	44	48,112	49	50,935	49	51,951	0	+1,016
Unobligated balance lapsing.....	—	19	—	16	—	11	—	—	—	—	—	—
Total, budget authority.....	52	45,530	53	46,789	44	48,123	49	50,935	49	51,951	0	+1,016

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Summary of Changes

1996 Estimated budget authority.....	\$50,935,000
1997 Estimated budget authority.....	\$51,951,000
Net Change	+\$1,016,000

	1996 Current		Change from Base	
	Estimate Base			
	Pos.	Budget	Pos.	Budget
	(FTE's)	Authority	(FTE's)	Authority
<u>Changes:</u>				
A. Built-in				
1. Intramural				
a. Within grade increases.....		\$250,000		+\$4,000
b. Annualization of January				
1996 pay increase.....		250,000		+2,000
c. January 1996 pay increase.....		250,000		+6,000
d. Payment for centrally furnished				
services.....		72,000		-11,000
e. Increased cost of laboratory				
supplies, materials and				
other expenses.....		322,000		+8,000
Subtotal.....				+9,000
2. Research Management and				
Support				
a. Within grade increases.....		2,318,000		+42,000
b. Annualization of January				
1996 pay increase.....		2,318,000		+15,000
c. January 1996 pay increase.....		2,318,000		+53,000
d. FECF				+1,000
e. Payment for centrally furnished				
services.....		1,011,000		-41,000
f. Service and supply fund				
increases.....		186,000		+4,000
g. Increased cost of laboratory				
supplies, materials and				
and other expenses.....		1,116,000		+22,000
Subtotal.....				+96,000

Summary of Changes (con't)

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.....	104	25,356,000	-12	-1,742,000
b. Administrative supplements.....	(15)	432,000	—	—
c. Competing.....	44	10,259,000	+11	+2,758,000
Subtotal.....	148	36,047,000	-1	+1,016,000
SBIR/STTR.....	4	996,000	—	—
Total.....	152	37,045,000	-1	+1,016,000
2. Research centers.....	6	1,873,000	—	—
3. Other research.....	22	1,958,000	—	—
4. Research training.....	209	4,258,000	-5	+31,000
5. Research & development contracts.....	3	848,000	—	-31,000
6. Intramural research.....	<u>FTE's</u> 4	644,000	<u>FTE's</u>	-9,000
7. Research management and support.....	39	4,309,000		-96,000
Subtotal.....				+911,000
Total changes.....				+1,016,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Authority by Object

	1996 Estimate	1997 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	49	49	—
Full-time equivalent of overtime and holiday hours.....	0	0	—
Average ES salary.....	\$107,684	\$110,420	+\$2,736
Average GMGS grade.....	10.5	10.6	+.1
Average GMGS salary.....	\$48,639	\$50,152	+\$1,513
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).....	\$67,883	\$67,883	—
Average salary of ungraded positions.....	\$62,250	\$63,830	+\$1,580
Personnel compensation:			
Full-time permanent.....	\$1,872,000	\$1,938,000	+\$66,000
Other than full-time permanent.....	146,000	170,000	+24,000
Other personnel compensation.....	14,000	18,000	+4,000
Subtotal, personnel compensation.....	2,032,000	2,126,000	+94,000
Personnel benefits.....	536,000	565,000	+29,000
Benefits for former personnel.....	—	—	0
Travel and transportation of persons.....	57,000	57,000	0
Transportation of things.....	7,000	7,000	0
Rent, communications, and utilities.....	177,000	180,000	+3,000

	1996 Estimate	1997 Estimate	Increase or Decrease
Printing and reproduction.....	66,000	66,000	0
Other services:			
Consulting services.....	65,000	57,000	-8,000
Project contracts.....	848,000	817,000	-31,000
Other services.....	93,000	93,000	0
Purchases of goods and services from Government Accounts.....	1,822,000	1,704,000	-118,000
Supplies and materials.....	38,000	38,000	0
Equipment.....	46,000	46,000	0
Insurance Claims and Indemnities.....	14,000	14,000	0
Grants, subsidies & contributions.....	45,134,000	46,181,000	+1,047,000
Total budget authority by object.....	50,635,000	51,951,000	+1,016,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Administrative Costs

	1996 Estimate	1997 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1).....	\$1,872,000	\$1,938,000	+\$66,000
Other than Full-time permanent (11.3).....	146,000	170,000	+24,000
Other Personnel Compensation (11.5).....	14,000	18,000	+4,000
Special Personnel Service (11.8).....	—	—	0
Total Personnel Compensation (11.9).....	2,032,000	2,126,000	+94,000
Personnel Benefits (12.0).....	536,000	565,000	+29,000
Benefits for Former Personnel (13.0).....	—	—	0
Travel (21.0).....	57,000	57,000	0
Transportation of Things (22.0).....	7,000	7,000	0
Rental Payments to Others (23.2).....	—	—	0
Communications, Utilities, and Miscellaneous Charges (23.3).....	177,000	180,000	+3,000
Printing and Reproduction (24.0).....	66,000	66,000	0
Consulting Services (25.1).....	65,000	57,000	-8,000
Other Services (25.2).....	93,000	93,000	0
Purchase from goods and services from Government Accounts (25.3).....	1,822,000	1,704,000	-118,000
Operation of GOCOs (25.4).....	—	—	—
Supplies and materials (26.0).....	38,000	38,000	0
Total.....	4,893,000	4,893,000	0

National Institutes of Health

National Institute of Nursing Research

1996 Senate Report LanguageItem

Managing Pain- ... The Senate in its report 104-145, page 95 states that the Committee strongly supports NINR taking the lead in a major NIH-wide research initiative that addresses both biological and behavioral aspects of pain.

Action Taken or To be Taken

In FY 1996, NINR continued as the lead institute on a program announcement entitled Biobehavioral Pain Research. Other institutes and offices collaborating in the program announcement included NIDR, NIA, NIAMS, NCI, NICHD, NIDA, NHLBI, NIMH, NINDS and the Office of Alternative Medicine. The purpose of this biobehavioral pain research program announcement was to stimulate and foster a wide range of basic and clinical studies on pain as they relate to the missions of these institutes.

Item

Genetic Testing and Gene Therapy- ... The Senate in its report 104-145, page 95 states compelling advances in molecular genetics are out pacing knowledge of the clinical implications. The Committee is concerned about this imbalance and expresses its support for NINR's increased collaboration with the National Center on Human Genome Research. Joint efforts are essential to develop and evaluate teaching and counseling methods that help patients and their families make informed decisions about whether to undergo genetic screening.

Action Taken or To be Taken

The NINR is supporting expanded programs of research in decision making and associated medical, social and ethical questions posed by genetic diagnostics and therapeutics. An interdisciplinary group of basic and clinical scientists will be convened to identify other opportunities for NINR in genetics research, which will set the stage for research, career development and research training activities over the next decade.

Item

Cooperation with the National Cancer Institute- ... The Senate in its report 104-145, page 96 states it continues to recommend that the NINR work closely with the NCI to develop research studies that address breast cancer - including symptom management, quality of life issues, and preventive screening. Action Taken or To be Taken

The NINR is collaborating with NIA and NCI on a Program Announcement on Aging Women and Breast Cancer.

Item

Minority Research- ... The Senate in its report 104-145, page 95 states that it encourages the NINR to expand the Malama Project and to further address other minorities in Hawaii.

Action Taken or To be Taken

This project is still ongoing and is anticipated to be completed in August 1996.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Authorizing Legislation

PHS Act/ Other Citation	U.S. Code Citation	1996 Amt. Authorized	1996 Estimate	1997 Amt. Authorized	1997 Estimate
Research and Investigation.....	Section 301				
National Institute of Nursing Research.....	Title IV, Part C	Indefinite	\$46,677,000	Indefinite	\$47,662,000
National Research Service Awards.....	Section 487 (d)	Such sums as necessary	4,258,000	Authorization is pending	4,269,000
Total Budget Authority.....			50,935,000		51,951,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Appropriation History

<u>Year</u>	<u>Budget Estimate to Congress</u>	<u>House Allowance</u>	<u>Senate Allowance</u>	<u>Appropriation 1/</u>
1987	—	\$16,700,000	\$20,000,000	\$20,000,000
1988	16,133,000	24,744,000 2/	23,566,000	23,380,000
1989	24,400,000 3/	27,417,000 4/	28,107,000	29,139,000
1990	29,970,000 5/	32,969,000	34,969,000	33,935,000 6/
1990 Sequester				-422,000
1991	35,127,000	37,289,000 7/	40,013,000	39,722,000 8/
1991 Sequester				-1,000
1992	43,747,000	43,143,000	45,880,000	44,970,000 9/
1993	48,568,000	47,383,000	49,000,000	48,119,000 10/
1994	48,975,000	51,018,000	51,018,000	51,018,000
1995 11/	48,326,000	47,971,000	48,326,000	48,180,000 12/
1996 11/	50,159,000	50,935,000	49,497,000	50,935,000
1997 11/	51,951,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research consolidated at the Secretary's level.

3/ The 1989 request excludes funds for AIDS research and education (\$707,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Excludes \$2,690,000 in NRSA training programs not considered.

5/ The 1990 request excludes funds for the National HIV Program (\$999,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ Excludes enacted administrative reduction of \$34,000.

7/ Excludes \$4,233,000 in NRSA training programs not considered.

8/ Excludes enacted administrative reductions of \$1,046,000.

9/ Excludes enacted administrative reductions of \$226,000.

10/ Excludes enacted administrative reductions of \$472,000.

11/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995, FY 1996, and FY 1997.

12/ Excludes enacted administrative reductions of \$19,000, \$1,000, and \$37,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Detail of Full-Time Equivalent Employment

	1995 Actual	1996 Estimate	1997 Estimate
Office of the Director.....	21	21	21
Division of Extramural Research.....	15	20	20
Division of Intramural Research.....	8	8	8
Total	44	49	49

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Average GS/GM Grade

1991.....	10.6
1992.....	10.7
1993.....	11.1
1994.....	11.2
1995.....	10.2
1996.....	10.5
1997.....	10.6

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Program Administration
Detail of End-of-Year Employment

	1995 Actual	1996 Estimate	1997 Request
ES-3.....	1	1	1
ES-2.....	—	1	1
Subtotal.....	1	2	2
Total - ES Salary.....	\$103,800	\$215,368	\$220,839
GS-15.....	4	5	5
GS-14.....	4	6	6
GS-13.....	6	6	6
GS-12.....	6	6	6
GS-11.....	3	3	3
GS-10.....	1	1	1
GS-9.....	1	2	3
GS-8.....	4	3	3
GS-7.....	4	6	5
GS-6.....	2	2	2
GS-5.....	1	1	1
GS-4.....	2	1	1
GS-3.....	2	2	2
Subtotal.....	40	44	44
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade.....	1	1	1
Senior Grade.....	1	1	1
Subtotal.....	2	2	2
Ungraded.....	2	2	2
Total permanent positions.....	38	43	43
Total positions, end of year.....	45	50	50
Total full-time equivalent (FTE) employment, and end of year.....	44	48	48
Average ES level.....	3.0	3.0	3.0
Average ES salary.....	\$103,800	\$107,684	\$110,420
Average GS/GM grade.....	10.2	10.5	10.6
Average GS/GM salary.....	\$46,264	\$48,639	\$50,152

TUESDAY, MAY 14, 1996

NOBEL LAUREATES BIOMEDICAL RESEARCH PANEL

WITNESSES

DANIEL NATHANS, M.D., JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

E. DONNALL THOMAS, M.D., FRED HUTCHINSON CANCER RESEARCH CENTER, SEATTLE, WASHINGTON

ERIC WIESCHAUS, M.D., PRINCETON UNIVERSITY, PRINCETON, NEW JERSEY

INTRODUCTION OF WITNESSES

Mr. PORTER. The subcommittee will come to order.

This afternoon we are pleased to repeat a subcommittee tradition that we first revived last year. As a cap stone to the year's NIH hearings, we have invited three Nobel Laureates to address the subcommittee to give us their perspective on biological research issues.

We are very pleased to have with us today Dr. Eric Wieschaus from Princeton; Dr. Daniel Nathans from Johns Hopkins; and Dr. Donnall Thomas from the Fred Hutchinson Cancer Center at the University of Washington.

Dr. Wieschaus received the Nobel Prize just last year. Dr. Thomas received his in 1990, along with one of the Nobel Laureates who testified last year, Dr. Joseph Murray; and Dr. Nathans received his Nobel Prize in 1978.

Dr. Nathans, welcome back for a second appearance before the subcommittee this year after your testimony at our public witness hearings in March.

I would also like to note that Dr. Varmus is in attendance in the audience and I thank him for his role in arranging this hearing as well as the NIH tour this morning for Members and staff.

If the three Nobel Laureates would like to proceed, we would be pleased to hear from you in whatever order you would like, and after each of you makes his statement, Members can address questions to you.

Gentlemen, please proceed.

DR. NATHANS' OPENING STATEMENT

Dr. NATHANS. Mr. Chairman and Members of the subcommittee, I am honored to testify together with my colleagues on biomedical research in the United States. We are very grateful to the committee for continuing this tradition of having leaders in biomedical research in the United States come to talk to you.

I think for all of us it may make sense to begin with talking about our own careers, how we began, because I think it is very similar to what young people face today as they begin careers in

biomedical research, and I think will also give you a flavor of what it means to do research, what discovery is about, and what the repercussions of those discoveries can be for the health and welfare of the American people.

CAREER HISTORY

I am Professor of Molecular Biology and Genetics and Senior Investigator of the Howard Hughes Medical Institute at Johns Hopkins University. This year I am also serving as interim President for the University. I was born in Wilmington Delaware, I went to the public schools, went to the University of Delaware and studied chemistry.

I then went to Medical School at Washington University in St. Louis, and did an internship and residency in internal medicine. I spent 2 years at the National Cancer Institute in Bethesda as a Clinical Associate in the Cancer Institute where I also did some research.

Incidentally, for that of course I was supported by NIH during those years and also thereafter when I became a postdoctoral fellow in biochemistry, I had a fellowship at \$7,000 a year, as I recall.

It is something I grew to love and decided to pursue a career in medical research rather than medical practice. And I went to Johns Hopkins as a member of the faculty. And, of course, that meant applying for a grant to NIH in order to support research that I had begun as a postdoctoral fellow.

In those days, this was in 1962, if one showed promise and had some interesting ideas to pursue, then it was almost certain that you would get support. In fact, a site visit team came up to visit me in order to find out whether the university was giving me enough space and time to do my research.

It was a wonderful time and it was a time when young people like myself felt they had the opportunity and it was really entirely up to them to show that they could be productive and do interesting things to qualify for a continuation of the kind of confidence that was shown in them that is reflected in getting the NIH grant.

So I began work on how protein molecules are made, work that I had started as a postdoctoral fellow. I taught medical students and graduate students and in the course of that teaching began to get interested in viruses that cause cancer in animals. This was as a result of an assignment to teach medical students about tumor viruses, and I decided to take a leave of absence.

I went to the Weizman Institute in Israel to learn about tumor viruses, and just about that time a colleague of mine at Hopkins discovered an enzyme called a restriction enzyme in bacteria that suddenly opened up the possibility of studying tumor viruses and other viruses; in fact, DNA in general, the genetic material in general, in an entirely new way.

RECOMBINANT DNA

I want to take a moment to tell you about these chemical scissors, as the restriction enzymes are called, to give you a little background to see how, by a scientist following his interests, something quite unexpected comes out of it very often. The discovery of restriction enzymes, which have become one of the fundamental tools

in recombinant DNA and modern type of genetics, came about because a scientist was curious about a phenomenon he discovered, namely how viruses grow inside bacteria. It was a very peculiar observation he made, that bacteria that were nearly identical but not quite, were quite different in whether or not they supported the growth of these viruses.

He discovered that those cells that did not support the growth of the viruses contained an enzyme that could recognize foreign DNA and break it down, in a sense, a primitive immune system that these organisms had. And as a follow-up to that, others were able to isolate these enzymes. And it turns out that there are now hundreds of them known which can cut up DNA in specific places and in that way analyze DNA in a new way.

I applied this to the study of a tumor virus and, in essence, this little virus which had a little piece of DNA as its genetic material could now be cut up and dissected into very small pieces which then led to the ability to completely analyze the DNA chemically to find all its genes, determine which genes are the ones responsible for cancer, study how that gene might cause cells to become cancerous, and in this way also lead to what is called DNA splicing, where you bring different genes together that you can grow in bacterial cells, and that is the whole recombinant DNA revolution.

I bring this up primarily to illustrate the point that frequently very fundamental nondirected research gives rise to quite unexpected discoveries that have immense implications for a broad understanding, including understanding disease processes like cancer, and of course with the recombinant DNA revolution, being able to understand these mechanisms in general.

So that quite unexpected outcome of the research that my forbearers did, you might say, as well as our own laboratory and people following, I think gives a flavor of what fundamental science can contribute in this case in the way of technology as well as understanding in regard to a particular problem.

So I am going to stop, and of course would be open to any questions, and particularly questions as well as about the NIH, about university involvement in our whole health research efforts, and rather than make a statement about that, I think I will let my colleagues tell their stories and then we can come back to that, if you would like.

[The prepared statement of Dr. Daniel Nathans follows:]

JOHNS HOPKINS UNIVERSITY

Office of the President

242 Gariand Hall / 3400 N. Charles Street
Baltimore MD 21218-2688
(410) 516-8068 / FAX (410) 516-6097

Daniel Nathans
Interim President

TESTIMONY OF DANIEL NATHANS Interim President of The Johns Hopkins University and Professor of Molecular Biology and Genetics Before the

House Appropriations Subcommittee on Labor, Health and Human Services, and Education
May 14, 1996

Mr. Chairman and members of the Subcommittee, I am honored to testify, together with my colleagues, on biomedical research and the FY 1997 NIH budget.

My name is Daniel Nathans. I am a professor of Molecular Biology and Genetics and senior investigator of the Howard Hughes Medical Institute at The Johns Hopkins University School of Medicine. This year I am also serving as interim president of the University.

I was born in 1928 in Wilmington, Delaware. I attended the public schools of Wilmington, the University of Delaware, and Washington University School of Medicine in St. Louis, receiving a B.S. degree in chemistry in 1950 and an M.D. degree in 1954.

Following a residency in medicine, I joined the laboratory of Fritz Lipmann at Rockefeller University. There I studied the biochemistry of protein formation and the synthesis of proteins encoded in the RNA genome of a bacterial virus. This natural messenger RNA became a widely used tool for unraveling the mechanism of protein synthesis and its regulation.

In 1962 I joined the faculty of The Johns Hopkins University School of Medicine, where I have remained to the present time. From 1972 to 1982 I served as Director of the Department of Microbiology. My research interests have centered on protein biosynthesis, viruses that cause tumors in animals, and cellular responses to growth factors. In our analysis of a model tumor virus, my students and I used restriction enzymes to construct physical and functional maps of



the viral genome, to compare genomes by "DNA fingerprinting," to isolate specific gene segments, and to modify DNA molecules at predetermined sites. This work aided the development of methods for cloning and sequencing DNA and for mapping human genes. For the application of restriction enzymes to problems of molecular genetics, I received the National Academy of Sciences Award in Molecular Biology in 1976 and shared the 1978 Nobel Prize in Physiology or Medicine with Werner Arber and Hamilton O. Smith. In 1993 I received the U.S. National Medal of Science and in 1994, the Milton S. Eisenhower Medal of The Johns Hopkins University.

In addition to my research, I have been a teacher of medical students, graduate students, and post-doctoral trainees and have served as an adviser to foundations, universities, government, and industry. I am a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society, and am an associate member of the European Molecular Biology Organization. From 1990 to 1993 I served on the President's Council of Advisers on Science and Technology.

First let me commend you, Mr. Chairman, and other members of the Subcommittee for your leadership that led to the FY 1996 budget for NIH. It has made an enormous difference, particularly regarding opportunities for young biomedical scientists, whose talents are essential to the continuing vitality of the American biomedical enterprise.

On March 7, 1996, I testified before this Subcommittee concerning the FY 1997 NIH budget on behalf of five biomedical societies: the American Society for Cell Biology, the American Society for Biochemistry and Molecular Biology, the Biophysical Society, the Genetics Society of America, and the American Association of Anatomists. That testimony is on the record, and I will not repeat what I said then.

Rather I would like to emphasize the following themes in my testimony today:

- NIH is a jewel in the federal government's crown. It has been a great success by any measure; e.g., fundamental and applied discoveries, impact on biomedical industry, international reputation of American science and science-based industry, and, most important, improvement in the health of the American people. Its future promise is enormous.

- The federal investment in biomedical research, though substantial, is a small fraction of the overall expenditure for health care in the nation. This investment has the potential substantially to reduce those overall costs, and has already done so in specific cases. Federal investment complements that of industry and cannot be replaced by industrial investment.

- Continued pre-eminence in medical science and related industry depends on attracting some of our most creative young men and women into careers in biomedical science. Many are now discouraged by the difficulty of finding support early in their careers.

- The federal-university partnership, coupling research and education, is the cornerstone of NIH's success. That relationship must be protected from damaging shifts in federal policy and from the revolutionary changes now occurring in the delivery of health care.

DR. WIESCHAUS' OPENING STATEMENT

Dr. WIESCHAUS. Mr. Chairman, Members of the subcommittee, in my testimony today, I would like to tell you about recent advances in our understanding of how genes control the way embryos develop. I am going to do this in terms of my own personal history, not only because it is, as I think for all of us, our own experiments that we know best, but also because it is true that our own personal histories illustrate how an interest in a basic scientific question can then have broader implications that I don't think we fully anticipate from the beginning of these experiments.

CAREER HISTORY

I grew up in Birmingham, Alabama, did my undergraduate work at Notre Dame. I think one of the central experiences of my own life was an undergraduate course where I saw living embryos, frog embryos developing right in front of me under a microscope and I knew I wanted to understand how embryos developed, how cells get directed to make particular structures and how they move into a particular region of the embryo that I wanted to understand.

Even though it was these very early events in development that had impressed me so much, it was clear to me at the time, that development as a process wasn't just limited to what happens in an embryo; that in fact everything that goes on in our bodies is a developmental process as our bodies make new cells to renew different organs.

DEVELOPMENTAL BIOLOGY

I think study of developmental biology has implications beyond just the way that an embryo develops. We know that embryonic development depends on genes and failure of these genes to function properly will cause abnormalities, will cause birth defects. The big difficulty that scientists faced over the past 20, 30 years is the enormous complexity of the genes, the DNA that is in our bodies.

There are, by some estimates, 100,000 different gene products in an embryo. The problem, if you want to understand development, the basic problem is to sort through these different gene products and identify the particular genes that are important, and to understand what it is that those particular genes do for particular steps and particular processes of development.

About 15 years when Christiane Nusslein-Volhard and I were young scientists starting on our own career, we were interested in development and we decided that we would try to tackle the question of gene activity in development. The strategy that we chose was to try to identify genes that control the way the fruit fly embryo developed.

If you asked us at the time we would have told you that we thought this was a basic research question, and I don't think either of us had any sense of the long-term implication of those experiments. We chose fruit flies because people had worked on them for 60 or 70 years.

There was a lot known about how to manipulate the genetics and also there was work being done by a man named Ed Lewis that suggested that it was possible to obtain mutations in genes that

would affect specific parts or specific regions of the embryo. What we were interested in was to try to use those techniques to obtain mutations to understand development more broadly.

What we reasoned was that if a gene was really essential to the way that a fly embryo developed, if we knocked out that gene, if we made a mutation of that gene, the embryo would develop abnormally. If the gene did something specific, most of the cells in the embryo would develop normally. Only certain cells would go wrong, and by looking at the genes that went wrong in each of those mutants, we would be able to extrapolate that to what the normal gene had to do to ensure normal development.

It seemed to us that to really understand development, we would just have to make enough mutations and look at them and analyze them. Over a period of a year and a half, Christiane Nusslein-Volhard and I made mutant fruit fly inbred lines, similar to inbred families, that would be carriers for a genetic disease. We made something like 27,000 little inbred lines, and these lines, we fed these flies mutagens. The chemicals we fed the flies were enough to induce 18,000 different mutations that were in genes that were essential at sometime during the life of the animal.

We asked how many of these genes were essential to the way the embryo develops. The first observation was that most of the genes weren't really essential; that if you looked for mutations that really changed the way embryos developed, all could be assigned to about 139 genes. That is a very small number, small enough for us to be able to analyze the abnormal development of each of these different mutant lines in some detail.

When we looked at the embryos, it was quite remarkable what we saw, because when one particular gene was mutated, the embryo didn't make a head. In another case the embryo didn't make muscles. In another case all the skin turned into nervous tissue. In each case when a gene was changed, the embryo generally developed normally, but there were specific abnormalities. By looking at those, we were able to reconstruct a picture of what all these different genes did during development.

At the time we did those experiments, we thought they were specific and were relevant for understanding how fruit fly embryos developed. When we published the experiments, they were well received by the scientific community because until that time no one had ever done a really careful survey of how genes affect development.

The real significance of these experiments, I think, became only clear in the 10 years that followed as laboratories all over the world began to study these genes. What has turned out to be true, and what I don't believe anybody anticipated 15 years ago, is that as each individual fly gene was cloned and its sequence analyzed, we found that very, very often the same gene wouldn't just be found in flies, but could be found in all living organisms. Very often we looked at that gene and tried to predict what that gene might be doing in controlling a very similar process.

So that has meant that those observations basically revolutionized the way that we think about development, the way we do studies of development nowadays; because what it means is that there is great similarity between all organisms on the earth, mean-

ing we can do experiments on animals like fruit flies and worms, that are easy to raise in the lab, easy to work with, and work through different kinds of problems. When we get an idea of how something works, what a gene actually does, then it is possible to try to apply that knowledge by working on animals that are more closely related to humans. There is an enormous efficiency in our ability to address very basic questions.

IMPORTANCE FOR BIRTH DEFECTS

When the Nobel Committee this past fall cited our work and the work of Ed Lewis for the Nobel Prize, it emphasized in its citation the importance of this work for birth defects. To a large extent it is true there are certain diseases, certain forms of human deafness, diseases that are known to be caused by mutations in these genes that were originally discovered in fruit flies, and there will be more and more cases of that kind of genetically controlled birth defect that will be analyzed by the procedures that I have outlined here.

But I think the even broader significance comes in the observation that these genes don't just function during embryonic development; that the same genes either continue to function in our bodies as an adult, or when they malfunction, they are associated with tumors and formations of cancer.

One of the striking things for me has been in the past 10 years the collaboration that has developed between scientists that are interested in developmental biology, the development of embryos, and scientists that are interested in cancers, because the same genes are involved. My own work, continues to be on fruit flies but a lot of that work is directed to genes that, when they are misexpressed in humans, are associated with tumors, and I am interested in understanding how they stick to each other, how they communicate with each other, how they control each other, their proliferation.

Throughout my scientific career, I have been supported by the National Science Foundation or NIH. As a graduate student I had an NSF predoctoral fellowship until I moved to Europe to complete doctoral studies. Since I moved back in 1981, my work has been supported by NIH.

If you would ask me to describe myself, I would describe myself as a basic researcher. What has been personally for me so exciting in the past 10 years is to realize how the developments in the field have made my work relevant not just for basic researchers, people who are interested in theoretical aspects of gene activities and embryos, but development broadly speaking. In fact, clinical issues will override.

I will stop there and maybe go on to another statement.

[The prepared statement of Dr. Eric Wieschaus follows:]

Congressional Testimony, May 14, 1996
Eric Wieschaus, Professor of Molecular Biology
Princeton University, Princeton, New Jersey

Mr. Chairman and Members of the Subcommittee:

In my testimony today, I would like to describe for you recent advances in our understanding of how genes control the way an embryo develops. This description will be presented in terms of my own personal history, not only because it is my own work that I know best, but also because those experiments reveal how research programs designed to address basic scientific issues can turn out to have unexpected relevance to human biology and thus potentially great clinical significance.

Since college I have been fascinated by the extraordinary process that converts an apparently simple undifferentiated egg cell into a complex organism with a wide variety of different cell types organized in a precise pattern. This process is called embryonic development and occurs in all animals and plants consisting of more than one cell. In all these embryos, the most dramatic transformations occur early in the process, when groups of cells are set aside to form specific organs and tissues and move to the right locations in the body of the embryo. Development however is not limited to just these early stages, or even to the nine months a human embryo exists in the womb. It continues through our adult life, as undifferentiated cells give rise to functional cells that renew most organ systems in our bodies. This gives understanding development an importance that extends beyond the embryo itself.

Embryonic development depends on genes. Failure of these genes to function causes abnormalities and birth defects. Until recently, however, very little was known about these genes in any organism. What made their analysis so difficult was their enormous diversity. Various molecular experiments have estimated the number of different gene products in the embryo to be somewhere between 10,000 and 100,000. Probably only a small fraction of these genes play essential roles in directing cells to particular cell

fates. The problem that scientists faced was to identify particular genes and sort out which gene products were essential for which steps.

Fifteen years ago, Christiane Nüsslein-Volhard and I were young scientists starting out on our own independent research careers. We were interested in development and decided to tackle the problem by identifying genes that were essential in fruit fly embryos. If you had asked us at the time, we would have described our experiments as purely basic research. We chose fruit flies because geneticists had worked on them for over sixty years and had established techniques for making mutations and mapping gene on chromosomes. We wanted to apply these techniques to development and reasoned that if a gene were essential, the fruit fly embryo would develop abnormally when that gene was mutated. If the gene played a specific role, most structures in the affected embryo would still be normal and the defects might be limited to specific regions of the body or specific tissues. Based on these defects, it should be possible for us to reconstruct the normal role of each gene. If we looked at enough different mutations, we would gradually be able to piece together a picture of how development occurred.

Over the course of a year we established 27,000 inbred fruit fly lines, each carrying randomly induced mutations. In a certain sense, these lines were like 27,000 inbred human families, each carrying its own inherited disease. The fly lines we established contained about 18,000 different mutations that caused the animal to die at some point in its life cycle. However, most of these mutations did not seem to affect embryos in any noticeable way. In fact, all the mutations that caused major embryonic defects could be assigned to one of 139 different genes. The smallness of this number made it possible for us to examine mutant embryos from each of the lines in some detail. The embryos from a particular mutant line might be missing heads, or didn't make muscles, or had all of their skin converted into nerve tissue. The striking nature of these defects suggested that these 139 genes functioned something like master regulators, each controlling a different, genetically defined step in normal development.

Although our initial experiments were limited to fruit flies and fruit fly development, they were received with great interest by the scientific

community. Up to that point such a complete survey of gene activities in development had never been carried out in any organism. The experiments assumed an even greater significance in the decade that followed, as many labs around the world began to study these genes. As each fly gene was cloned and its sequence analyzed, it became clear that very similar DNA sequences (i. e., similar genes) could be found in organisms other than flies, even in humans. Moreover, the role these genes played in development seemed very similar regardless of the organism. Over the past ten years we have gradually come to a realization of the enormous similarity in the genetic make-up of all organisms on this earth. This similarity has had great impact on the way science is done. It makes it possible to address many basic questions in simple organisms like flies and worms that are easy to work with in the lab. Once a basic process has been analyzed in such "model" organisms, it is possible to re-examine the phenomenon in animals more closely related to man. In this way, we believe it will ultimately be possible to understand how even complicated processes in our own bodies work.

In its 1995 citation for this work, the Nobel Committee emphasized its significance for human development and birth defects. We now know that certain forms of human deafness, called Waardenburg syndrome, are caused by mutations in genes that were first identified in flies, and some forms of spina bifida in mice are associated with mutations in others. The number of such cases is still relatively small and probably reflects the recentness of the discovery. There will certainly be more examples as we learn more about human development. More importantly, by understanding how genes control development, we will be in a better position to address all aspects of clinical importance in development, even those defects that do not seem to have immediate genetic causes. The work's significance however may not be limited only to birth defects. Over the past ten years, we have gradually come to realize that many of the genes that control development continue to function at later stages. Others cause cancers and over-proliferation when they are mutated or mis-expressed in adults. One of the fascinating developments in science over the past ten years has been the close collaboration between scientists working on development and those working on cancer. Although I continue to work almost exclusively with fruit flies, much of that work is directed at understanding how genes whose mis-expression causes tumors in

humans function in normal cells to control their adhesion to each other and their rates of proliferation. As a scientist I have always been driven by my interest in basic questions. I am in that sense a typical example of a basic researcher. One of the exciting aspects of the age we live in is that never before has basic research had the potential to impact so immediately on questions of clinical importance.

DR. THOMAS' OPENING STATEMENT

Dr. THOMAS. Mr. Porter and Members of the committee, as you have heard, my name is Don Thomas. I work at the Fred Hutchinson Cancer Research Center in Seattle at the University of Washington. My personal story and my interest in medicine goes back to a time earlier than I can remember because my father was a general practitioner in a small town in Texas, and I grew up helping him and making house calls with him. He died in 1941, and I graduated from Harvard Medical School in 1946.

CAREER HISTORY

It is interesting to contrast his 50 years in medicine with my 50 years in medicine. They are almost totally different. Things that we take for granted, like insulin and the first antibiotic, came along in the last decade of his career in medicine. All this, of course, is a result of research over the years.

In 1950, I received a National Research Council fellowship, which made it possible for me to have a postdoctoral year in the biology department at MIT. I went back to the Brigham Hospital in Boston, and Sidney Farber gave me a small laboratory in the old Jimmy Fund building, which is the precursor of the Farber Cancer Building, and I received in 1952 my first research grant from the NIH. It provided me with enough money for a technician and to run my laboratory for a year, and the amount of that grant was \$6,000. How times have changed.

In 1955, I went to the Mary Imogene Basset Hospital in Coopers-town, and just about that time some work by others in inbred mice had suggested the possibility that bone marrow transplantation, at least in inbred mice, might be feasible. We began to do research in bone marrow transplantation with some support from the NIH, and also support from the old Atomic Energy Commission. They supported us because of the concern about radiation accidents and so on.

In our clinical studies in those days, we had no success except for an occasional patient with leukemia who happened to have an identical twin where tissue typing, of course, had already been done by nature.

Also, in 1955 we began studies in the dog as an outbred animal, available in large families, susceptible to clinical maneuvers, and particularly valuable in bridging knowledge from inbred mice to application to our human patients. We continued that work actually for over 15 years.

In 1963, I was offered a professorship in medicine at the University of Washington and moved there, and I happened to be very lucky at that time because I received one of the very few research career awards. Some of you may remember that in 1962 and 1963, the NIH had decided to award a few lifetime grants, and I was fortunate to receive one of those. The amount of that grant was \$25,000, not very much perhaps by present standards, but it provided a base for my salary, and particularly it required a commitment from my institution to make my time free for research.

In 1967, work in animals, mice and dogs had progressed to the point where we thought that human marrow transplantation should be undertaken. We wrote our first program project grant, which was funded in 1968, and at about that time the knowledge of human tissue typing done by others had progressed to the point where we could begin again to do research in marrow grafting in human patients, particularly patients with end stage leukemia.

I will use the term "we" periodically because at about that time many investigators joined in this, and in those early days, particularly Dr. Robert Good, then at Minnesota, and Dr. George Santos at Johns Hopkins.

As success improved, there was a much wider application of marrow transplantation to different diseases, particularly in early treatment before patients reached the very end stage of their disease. At present there are more than 200 institutions in the United States that carry out bone marrow transplants.

In 1990, after Dr. Murray and I received the Nobel Prize, then-Secretary Louis Sullivan had a reception at the NIH to honor our prize, and he had had his staff calculate that over a 30-year period our team had received \$673 million in research. That is, of course, a lifetime of research, a large sum of money, but it would have been impossible to do this if we had not had that kind of support.

Of course, we made detours into laboratory research, immunology, radiation biology, cell biology and more recently molecular biology, but our focus was always on application to human patients. This is clinical research.

I would make a few comments about clinical research, that clinical research and animal research are really inseparable. I would quote from my Nobel address, with your permission.

Finally, it should be noted that marrow grafting could not have reached clinical application without animal research first in inbred rodents and then in outbred species, especially the dog.

I mention this because I think we must resist the well-meant, well-intentioned people who are opposed to animal research. Certainly animal research should be done in the most humane possible way, but we should guard against regulations that make it impractical to do this research with animals.

In my written statement I have addressed a few other things that I won't talk about right now. One, of course, is clinical research itself; the position of young investigators who want to go into clinical research, and particularly access to patients for research now being blocked by insurance companies and HMOs, and so on. And I won't talk about the problem of priorities that this committee has to struggle with.

I know that we are all very reluctant to pass on debts to our children, but I would point out that the principal beneficiaries of present-day medical research will be our children and our grandchildren, and we shouldn't lose sight of that.

Finally, in the testimony here by others, and by my colleagues now and by Dr. Varmus, you have heard of these exciting advances in many aspects of biomedical research of how the cells in our bodies function at the molecular level, how these cells talk to each other, something about what goes wrong when disease occurs, and I am actually hopeful that in my lifetime improved methods of treatment or prevention will make marrow transplantation as we now know it obsolete.

Thank you for the privilege of being here.

[The prepared statement of Dr. E. Donnall Thomas follows:]



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RESEARCH
CENTER

May 14, 1996

Testimony of: E. Donnell Thomas, M. D.
Member, Fred Hutchinson Cancer Research Center
Professor of Medicine, Emeritus, University of
Washington

Thank you for the privilege of appearing before this committee. In 1990 I shared the Nobel Prize in Medicine with Dr. Joseph Murray, who appeared before this committee last year. Our prize was for the early work in transplantation--kidney and bone marrow.

Let me begin with a personal note. My father, who died in 1941, was a general practitioner in a small Texas town. I fell in love with medicine through assisting him in his office and accompanying him on house calls. He was highly regarded in our community, but, in retrospect, his ability to provide effective treatment was pitiful. Many of the drugs that we take for granted today, such as insulin and sulfonamides, came along near the end of his career. I graduated from Harvard Medical School in 1946. My 50 years in medicine have seen changes that my father could never have imagined. My own field of marrow transplantation did not exist at the time of his death, but now world-wide more than 20,000 marrow transplants are done each year with resulting cure of a wide variety of previously incurable diseases, including leukemia and genetic disease of the bone marrow.

In 1950 I received a National Research Council fellowship which allowed me to spend a year at M.I.T. in the biology department. In 1952 I received my first small grant from the NIH, a project to study some biochemical aspects of bone marrow metabolism. Dr. Sidney Farber had given me a small laboratory in the newly-constructed Jimmy Fund building, now the Dana-Farber Cancer Center in Boston. The grant was for \$6,000, enough to pay one technician and run my laboratory for a year. How times have changed!

In 1955 my colleagues and I in Cooperstown began to work on transplantation of bone marrow in human patients following the lead of others who had demonstrated the possibility of such transplantation in inbred mice. Some of our first funding came from the Atomic Energy Commission because of the interest in marrow transplantation for treatment of irradiation victims. We received further support for our basic studies of the marrow from the NIH. We had no success in our attempts at human marrow transplantation for patients with terminal leukemia except for an occasional patient who had an identical twin to serve as marrow donor.

At the same time we began studies in the dog as an outbred animal to bridge the gap between studies in inbred rodents and application to our human patients. For 15 years we did most of our work with dogs studying the multiple problems of marrow transplantat'ion. We showed that tissue matching was essential for successful transplants even between littermates.

In 1963 we moved our program to Seattle. I was one of a lucky few to receive a Career Research Award from the NIH which not only assured my salary but also committed my institutions to protecting my time for research. By 1967 we were convinced that enough was known about human tissue typing so that we should return to human studies. In 1968 our first program project grant was funded by the NIH and we resumed our human studies in 1969. Those were difficult years because many thought that marrow grafting would never reach the point of general clinical application. By 1975 we had demonstrated that we could cure some patients with terminal leukemia which made it ethically possible to consider transplantation earlier in the course of the disease and to carry out marrow transplants for other diseases.

The last 20 years have seen a world-wide application by many transplant teams of marrow transplantation for a variety of malignant or genetic diseases as yet not curable by any other approach.

In 1990 Secretary Lewis Sullivan, at a reception at the NIH honoring the Nobel Prize, announced that my colleagues and I had received approximately 63 million dollars in support of our research over a 30 year period. We could not have succeeded without that support.

Although our research has involved major detours into the laboratory in areas of immunology, irradiation biology, cell biology and, more recently, molecular biology, our work has always been directed to problems in human patients. Let me, therefore, address some of the major points in the area of Clinical Research.

1. Clinical Research: Clinical research involves patients with disease. The first and most important requirement is that patients participating in research must receive the very best care by highly trained physicians and nurses supported by the best of modern technology. The major objective of clinical research is to translate knowledge from the laboratory to clinical application. Therefore, those in charge of the patient must have an intimate knowledge of the laboratory sciences that are being applied to the patient.

2. Young Investigators: A clinical researcher must be skilled in both medicine and laboratory science. The demands on such a person are enormous--medical school, clinical training, subspecialty

training (in my case, hematology and oncology), laboratory training followed by development of a research program. We must continue to encourage and support our brightest young investigators who will be the leaders in clinical investigation in the decade to come.

3. Patients for Research: Rapid changes in medical care in this country are creating major problems in clinical research. Insurance companies and HMOs are resistant to having patients treated by any means other than established therapy. Yet, it is obvious that if patients are to receive the benefits of our research, we must at some point apply that research to patients. What are the solutions:

a) Require that third party carriers provide clinical coverage for patients being studied on approved protocols (approved by the NIH, the NCI or the regional cancer centers).

b) Make funds available so that the NIH and the NCI can cover those costs that are related to the research. In the 1960s and 70s we were able to get significant support from the NIH for care of research patients but in recent years those funds have been essentially eliminated.

4. Animal Research. Animal research is an absolute requirement for transferring new knowledge from the laboratory to the patient. Both Dr. Murray and I made that point in our Nobel addresses. I stated "Finally, it should be noted that marrow grafting could not have reached clinical application without animal research, first in inbred rodents and then in outbred species, particularly the dog." We must resist those well-meaning individuals who are opposed to animal research. Certainly, animal research must be done in the most humane manner, but we should be careful that regulations do not become so restrictive as to eliminate the possibility of life-saving research.

5. Priorities. In this time of increasing fiscal restraints and the recognition that we should not pass on financial obligations to our children, the most important question concerns our priorities and the sums to be spent. The burden of answering that question falls on the shoulders of this committee. The desirability of control of disease and improving the duration and quality of life is obvious. In the long run, the only way to reduce the costs of medical care lies in better treatment and prevention of disease. A secondary benefit of our leadership in biomedical and pharmaceutical research has resulted in employment at home and economic benefits from sales abroad. We should keep in mind that the major beneficiaries of the biomedical research of today will be our children and grandchildren.

Finally, in the course of your hearings, testimony of Dr. Varmus and many others has outlined the exciting advances that are being made in our understanding of how the cells in our bodies work at the molecular level, how they communicate with each other, and something about what goes wrong in disease. I am hopeful that even in my lifetime improved methods of treatment or prevention will make marrow transplantation as we now know it obsolete.

Thank you again for the privilege of being here today.

Mr. PORTER. Let me thank each of our three Nobel Laureates for their statements.

We apologize that not more Members are present, but unfortunately, votes do not occur until 5:00 p.m. today and it is difficult to get Members to come back from home for anything prior to the time votes occur.

My first question is not for any one of the three. My first question is for the Deputy Director of NIH, Ruth Kirschstein, who said she wouldn't be here, and I am wondering who is minding the store.

Dr. KIRSCHSTEIN. It was a short ceremony.

Mr. PORTER. Welcome.

We are delighted you could be with us.

FRUIT FLIES AND MAPPING GENES

I think you are likely to hear a lot of different kinds of questions, curiosity questions, some of them. Dr. Wieschaus, fruit flies are the best model to use because they have a very short development and life-cycle, I assume, so you could see the changes very quickly; is that part of it?

Dr. WIESCHAUS. Part of it. That was probably the reason why 60 or 70 years ago people began working with fruit flies. I think the reason why most of us work with fruit flies today is that people have worked with them for 60 or 70 years and there is such an enormous amount known about them.

All the techniques are established for mapping genes, for doing the kinds of experiments that I described. Also animal husbandry aspects of raising 27,000 little individual inbred families were worked out simply because so many other research scientists have used those flies. I think you might find an organism that had a faster generation time or offers other special advantages, but it is very hard to balance out the enormous advantage of 80 years of previous work.

Mr. PORTER. As part of the Human Genome Project we are not only mapping the human genome, but more than that, we are mapping some rodents. One of the things that fascinated me, and you mentioned this in your remarks, was the close sharing of genetic material between human beings and animals and insects.

What I thought you said, if I understood it correctly, was that the same gene is found in perhaps all life.

Dr. WIESCHAUS. Yes.

Mr. PORTER. Is that true?

Dr. WIESCHAUS. Yes. I would say that to a large extent that is true, meaning, and I will qualify it, a particular gene that we identified in flies that would be necessary for flies to make muscle, it turns out that once that gene was identified—the piece of DNA from the fly was identified, that DNA sequence could also be identified in many other animals, all the way up to humans.

And if you look to see where that gene is expressed, it is also expressed in muscles. That suggests that that particular gene, the human gene and the fly gene are chemically very similar although they are not quite identical. They are probably doing the same things in both of those tissues.

In some cases, you can test that. If you have a fly mutation where the fly embryo doesn't develop normally because it lacks a gene, and you have identified a similar gene in a human, you can take out that human gene and use it to rescue, to save the fly embryo. That tells you that the human gene can function in the human the same as it can function in the fly. And there are 50,000 genes in the humans, not all have been identified, I can't tell you that—

Mr. PORTER. How many?

Dr. WIESCHAUS. 50,000.

Mr. PORTER. Is there the same number in fruit flies?

Dr. WIESCHAUS. There are probably 20,000 in fruit flies, so we win in that respect. We have maybe twice as many.

Mr. PORTER. My understanding is that it may be that, for example, the similarities in genes between human beings and a mouse, that maybe 90 percent of the genes would be the same and only 10 percent would be different, or something like that?

Dr. WIESCHAUS. That would be a good estimate. Part of the problem with all those estimates is that they reflect what we don't know. They are guesses. There are genes that we have worked with in flies where at the moment we have not been able to identify a comparable gene in humans. That may mean just at this point there isn't enough data available on human genes. So based on that lack of knowledge you make some guess about how similar these genomes are going to be.

I think the real emphasis of my statement and the major change in our thinking over the past 10 years is that 10 years ago I don't think any of us would have guessed how similar everything is, and now we are surprised when we don't find an immediately analogous gene in humans. Right now the whole picture has changed. Basically things are very similar.

What that probably means is that in the course of evolution you haven't come up with many new solutions. Many, many millions of years ago the basic ideas for how proteins work, the basic ideas for how genes work were established before the animals on this earth started diverging.

IMPORTANCE OF ANIMAL RESEARCH

Mr. PORTER. But what it means in practical terms is that the animal research is very, very relevant and important for its effect on human health?

Dr. WIESCHAUS. Absolutely.

Mr. PORTER. That is what Dr. Thomas was saying.

Dr. Thomas, in saying that, I am sure you realize, perhaps better than we do, but the strongest lobby around, if you ever want to face a lobby, is the Animal Welfare Lobby, for want of a better term. They are very, very strongly organized, and I am sure make some difficulty for research scientists as you attempt in the most humane possible way to use animals in your research.

Is there any—people don't focus on insects, but they do on dogs and other animals. Is there any real difference in—since we are talking about their genetic makeup, doesn't an insect feel pain the same way that a dog would feel it, for example?

Dr. WIESCHAUS. It is hard to know how a dog feels pain. Insects clearly have a nervous system. They clearly respond. If you touch them, if you put them in an uncomfortable situation, they try to crawl away. We know that by observing.

I think that the real issue is that most of us have never had a pet insect, and our affections—we like our dogs, and it is that many people don't even realize that insects are animals.

Mr. PORTER. When I went to China in 1981, I saw a little boy who had a bumblebee, with a string around it, attached to his finger. It was his pet. So there are some pet insects somewhere in the world.

Dr. NATHANS. I think there is another dimension to your question about similarity. Recently the entire sequence of the yeast genome became public, and there was a remarkable number of genes that had homologies similar to human genes. I bring this up in the context of what it is important to study that is relevant to human health, because it turns out this simple microbe, baker's yeast, is a model organism for studying genes that are closely related to our genes.

For example, in my own laboratory we came up with a mammalian gene that turned out to have a counterpart in yeast that is about 85 percent identical in its makeup. So we can now take advantage of all that is known about this simple microbe, yeast, including now its entire genomic sequence, to study how this protein acts, what it really does, and the parallel is very close. So it is a good reason to have invested so much in the study of this simple microorganism, because it contributes a great deal to understanding higher organisms.

BASIC VERSUS DIRECTED RESEARCH

Mr. PORTER. Dr. Nathans and Dr. Weischaus, and I am not sure about Dr. Thomas, but for the first two of you, your research could be described as fundamental or nondirective when you began it. We are getting to the place where we are discussing whether we should have much more directed research and look for an end result or product to research rather than to simply see where it leads us.

This is probably a result of the budgetary times in which we find ourselves more than anything, but could each of you, if you wish to, comment upon that direction and what you see as its pitfalls, if any?

Dr. WIESCHAUS. Obviously—you need to have both directed and pure basic research. My only immediate reaction is that in terms of yield per dollar, I think basic research probably has to have a greater yield simply because people who do basic research choose the organisms, they choose the question, they choose the particular cells they are going to work with most efficiently, and most directly ask some question about how cells work.

Whereas if you are dealing with human disease, you are saddled with the fact that you are working with humans, and all of the difficulties and all the lack of things that we don't know. So clinically-oriented research is much, much more difficult, and its success rates are going to be inevitably much lower, whereas I think basic research for the same dollars produces more information that is of long-term significance. You have to weigh that against all the other

considerations. But I think in terms of dollar yield, basic research would win.

Dr. NATHANS. I would say that you clearly need a balance. And the question is what is the appropriate balance, and it is not an easy question to answer. I think there is sometimes a mistaken notion that we have now accumulated enough basic information and that all we need to do is apply it, but that is not the way science works. There is a great deal we don't know and don't understand.

We won't know tomorrow whether some basic discovery is going to completely change the way we approach this disease or that disease, or perhaps many at once. So I think it is important that non-directed research, where it is basically curiosity-driven, be supported, because we simply cannot tell what is going to be discovered in the future that is going to make a big difference.

On the other hand, I think there are specific problems, particularly those that are reasonably well-defined, and we feel there is a base of fundamental knowledge to support a directed approach where it makes a great deal of sense, and obviously the American people, as they should be, are concerned about the ailments that they are all suffering now. So we clearly need to pay attention to that.

One thing that concerns me is that we not try to rush into something where there is not enough basic understanding of what the questions are and how to get the answers, because I think there we could use up a lot of money very unwisely

DIRECTED RESEARCH

Dr. THOMAS. I think this question of directed research is very difficult to define, who directs it and in what direction. There is such a network of interaction between what on the surface might appear to be different kinds of research. Our own efforts, for example, in transplantation biology and transplantation immunology get us into very basic areas of immunology, opportunistic infections which we encountered before AIDS ever appeared on the scene. But many aspects of immunology transplantation are comparable to those of autoimmune diseases so that I could say we are doing research in autoimmune diseases. This relates to rheumatoid arthritis, so we are doing research on arthritis. This relates to diabetes, which has an immune component, so we are doing diabetes research.

I think in directing research it is very hard to draw borderlines, and the real path to choose, I think, is one that we might call a path of opportunity where scientists think they can really do things that would give meaningful results. I think Dr. Varmus and his committees at NIH are in a unique position to make those determinations.

Dr. NATHANS. Could I just add one other thought? I think what we have seen happen in my field in molecular biology and genetics is a collapse of the time between fundamental discovery and the application. This occurs every day with discovery of genes that may turn out to be targets for new drugs, for example, or new hormones that may turn out to have therapeutic benefits. So the time between initial discovery, which you might call fundamental science because it was not directed toward the kind of therapeutics that I

mention, suddenly opened up new possibilities which are very quickly followed up.

Mr. PORTER. Thank you.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Gentlemen, at the outset let me say how much I appreciate the presentations that each of you have made here this afternoon. We were helped to understand your presentations a little better by having had the opportunity this morning provided by Dr. Varmus and Dr. Kirschstein for us members of the subcommittee to tour the National Institutes of Health and get an opportunity to see the application of the kind of research, particularly in the area of genes, that you have testified to here this afternoon. In fact, our Chairman was very modest. He didn't tell you that he actually used a laser beam to split a gene this morning in front of all of us. I can understand his modesty in front of a group of Nobel Laureates.

ATTRACTING PEOPLE TO CAREERS IN BIOMEDICAL SCIENCE

Let me start, Dr. Nathans. In your prepared testimony you make a very interesting comment. You tell us that continued pre-eminence in medical science and related industry depends on attracting some of our most creative young men and women into careers in biomedical science. Many are now discouraged by the difficulty of finding support early in their careers. Is this a very real problem as we sit here today and enjoy the benefits of testimony from three Nobel Laureates? As we look down the line, are we impacting on the future of seeing further American Nobel Laureates because of this problem that I highlight?

Dr. NATHANS. I would say it is absolutely real. I have had a lot of students in my day, postdoctoral students, who are looking for jobs when they have finished their training. It has become extremely difficult for my students, for students of my colleagues, to find suitable jobs. Our department recently had an opening for an assistant professor. I think we got about 250 applicants, many first-rate people.

It is quite real, and I think what we have seen happen in the way of the number of American Nobel Laureates in medicine and physiology is directly related to Federal support for research during the time when we were all growing up. So I don't think there is any question that if we can't support fresh young people with new ideas, who have a new perspective on things, that we are in serious trouble for the future.

Mr. STOKES. Thank you.

FUTURE OF MARROW TRANSPLANTATION

Dr. Thomas, I have found your contrast to what occurred in medicine during the 50 years of your father's practice and then the drastic radical changes you have seen in medicine over the 50 years that you have practiced to be a very, very interesting factor. I guess it brings me to the question I really want to pose to you.

In your statement you say, "I am hopeful even in my lifetime improved methods of treatment or prevention will make marrow

transplantation as we now know it obsolete." I think that is a very interesting factor.

Can you elaborate and tell us what you anticipate will occur in the future?

Dr. THOMAS. Well, for example, we still don't know what causes leukemia, and I think right now, we are beginning to have at least an increasingly clear body of information concerning some of the changes in the chromosomes that are associated with leukemia.

The first exhibit of that was chronic myeloid leukemia, but now we have certain translocations in others. We know that some abnormal proteins are the end result of this. I am very hopeful that sometime—next year, in the next 10 years—we will know enough about those changes to make them of therapeutic value. In fact, a good deal of research of that nature is going on at the present time.

I would like nothing better than to have, for example, a specific nonsense RNA, if you want, that blocks the 9;22 translocation in chronic myeloid leukemia, so that we wouldn't have to do bone marrow transplants for that disease.

I am sorry that Mr. Young is not here. You may know that he was a strong supporter of the national marrow donor program, and only later did his daughter develop chronic myeloid leukemia, and she had a bone marrow transplant. So this particular story would be very relevant to his personal experience.

But I would like, and I hope, that this knowledge of the basic molecular rearrangements will make it—get us to the point where we don't have to do bone marrow transplants for people like his daughter.

Mr. STOKES. You are right, Mr. Young has done a great deal of work in this area.

Dr. THOMAS. Yes, sir.

Mr. STOKES. We really applaud him for what he has done.

Let me take one further question before I move to Dr. Wieschaus.

FUTURE OF BIOMEDICAL RESEARCH

Considering the type of changes that you said that have occurred in your 50 years as opposed to 50 years in your father's private practice, what do you think, down the line, we can anticipate over the next 50 years occurring?

Dr. THOMAS. I am sure the other Nobel Laureates here will share my problem in that, when they handed out the Nobel Prize, they didn't give crystal balls to go with it. And so predicting the future, of course, is very difficult.

Mr. STOKES. Sure.

Dr. THOMAS. But we could cite individual examples—I have cited one, chronic myeloid leukemia, but there are many others. One problem, of course, with research is that you don't know the answer; that is why it is research. At some point these things become developmental engineering, if you will, and in some of these areas, I think we are entering the engineering phase. I think it is very difficult to predict the rate at which this will occur, except to go back and emphasize what Dr. Nathans has just said, that the conduct of this research and these advances will depend on our taking the very brightest young physician-scientists, and Ph.D. scientists, and supporting them so that they can do this work.

Mr. STOKES. Dr. Wieschaus, at the close of your statement, you tell us that one of the exciting aspects of the age we live in is that never before has basic research had the potential to impact so immediately on questions of clinical importance.

When we were at the institute this morning, we saw the machine that has been developed as a result of the gene splicing research, and one of the questions I posed was how long would it be before we see this out in the hospitals throughout the country and so forth. In this particular instance, we were exposed to the discovery of premalignant cancer genes, and we were told that in about six months we will see this on the market and in the various hospitals.

Taking your statement there, do you want to just enlarge upon when you see here?

Dr. WIESCHAUS. What I see as the immediate outcome, and I will talk again from my own research—when you identify genes that are involved in a particular process, sometimes knowing what those genes are, is useful because you can begin thinking about some type of genetic therapy. But I think the more immediate usefulness is that when you know the genes involved in a process, you can begin to investigate or understand that process.

One of the curious things that happened in my own research was that I thought I was working on a gene that controlled the way embryos developed, and when that gene was mutated, the embryo showed a particular kind of abnormality. But it turned out there wasn't just one gene, there were several genes that when you—that all produced the same kind of abnormality; and when those genes were cloned, it wasn't clear just looking at the cloning that these genes would in any way interact with each other. But it turned out that one of these genes was a major player in human cancers, and now we know that and a major goal of a lot of this research is to try to piece these different genes and these different proteins together so that we understand how the tumor's overproliferation occurs in cancerous cells.

So I think that the big yield is in terms of suddenly understanding how these cells work and then to be able to say now that we know how they work, now that the genes have told us how the cells work, can we think of a strategy, can we think of a drug, can we think of any procedures that would allow us to work around this particular disease? Those are not, admittedly, specific predictions of what immediate product is going to come from that research, but, the impressive feature is to suddenly know how these genes are connected to each other and how the parts of the cell are connected to each other. Until we know those kinds of facts, we are not going to develop reasonable strategies for big problems like cancer.

Mr. STOKES. Thank you very much.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Mr. Miller.

HEALTH CARE DELIVERY

Mr. MILLER. It is a pleasure to have you all here today. It is very exciting to have three such distinguished people with us.

Just to follow up on Mr. Stokes' question about, the "crystal ball" I know it is hard to look at the future, but we were out at NIH

this morning, at the Cancer Institute and the latest things happening there, and talking to Dr. Fauci.

And then prior to coming to this meeting, I was with a representative of the American Hospital Association, talking about health care in the future with Medicare and Medicaid and the cost of it, and the role of a general hospital in the future.

Hospitals are becoming intensive care units only. With fewer beds than the newer ones. How do you look at it from a cost delivery standpoint? I mean, kind of like in cancer, they are talking about the ability to use genes in the testing of precancer cells and the impact of that.

How do you—using your “crystal ball”, which you all have a hard time doing, but using that to say, well, the delivery of health care a decade from today is going to be very different, along with the role of specialists, the role of the hospitals.

I know you are in the research area rather than in the delivery of health care per se, but would you comment about, you know, the implications of this to the delivery of health care and the total cost of health care 10 years, 20 years from today, the research? Because the Speaker talks about it often. He believes, for example, in our next millennium that we are going to have some historic changes in the way health care is being delivered, and that it is going to have major impacts on the cost of health care. Can you go back to your crystal ball?

Dr. THOMAS. Well, of course, there are major changes in the way health care is delivered and its cost aspects. New technology comes along and it is more expensive initially. It usually drops in price as time goes on. Maybe this is a good opportunity to elaborate a little more on what I mentioned about patients for research.

Right now, if we have a patient who is a candidate for a new form of treatment, we have lots of problems. You know about the problems with autochthonous marrow grafts for patients with breast cancer where insurance companies have been very unwilling to pay for that. More and more HMOs, of course, are—it seems almost as though their only objective is to reduce costs and that is commendable, but it may not help the patient.

Wherever we are going with all of this, I don't know. I would simply say that I think we need some better support, some mechanism for support of patients that are undergoing new forms of treatment. Maybe we don't call it experimental; we call it new forms of treatment, which we think will be better than old forms of treatment.

NIH CLINICAL RESEARCH CENTER

In 1993 I testified before the Harkin-Hatfield committee about their proposal of a basic contribution to clinical care—in other words, insurance companies, HMOs, to research. Unless something like that is done. I have major concerns about how we will apply any of this new information, which gets me to a subject that I know that you have been concerned with, which is the cost of the proposed construction of the new clinical research center here at the NIH. I am sure in academic medicine we could make an argument against it in that there are bids being reduced in other centers; perhaps it would be cheaper to do this in other centers.

But I really come down very strongly in favor of building this clinical research center. We must do that, because in a few years, the way things are going now, that may be the only place in the country where we can do clinical research. This is a time of change; everybody is concerned about cost, but we mustn't lose sight of the fact that our present therapy is not—it is much greater than during my father's time, but we still have a long way to go, and ultimately, this element of basic science is going to have to be translated to our clinical patients, to our own families who get sick.

Dr. NATHANS. Mr. Miller, may I comment on that?

Mr. MILLER. Yes, please.

EFFECTS OF RESEARCH ON COST OF HEALTHCARE

Dr. NATHANS. I am far from an expert on the matters that you raise, but during the past year I have been rather heavily involved in discussion of these issues at Johns Hopkins. It is clear that there is a revolution going on in the way health care is delivered. Things are changing so rapidly, it is extremely hard to know how they are going to turn out.

Academic medical centers are at great risk in the face of all of these changes in which cost becomes perhaps the only criterion of success. And because it is clear, we have research costs and we have education costs which private managed care organizations do not have.

But I think—but maybe what your question was getting at is, will all of this research help to bring down the costs of health care? I think we can say it already has in many particular instances, and I think it is likely to continue to do so, although I would be the first to admit I can't tell you when that will occur, defined as some percentage drop in the health care costs of the Nation. But what we see is an increasing movement toward prevention, toward early detection of disease, not waiting until somebody gets a stroke, but trying to do something about the development of atherosclerosis in the general population; and I think that is going to have a major impact.

Now, that takes also a lot of research to figure that out, what to do to prevent atherosclerosis, for example, and therefore to prevent or delay strokes and heart attacks and the other consequences of atherosclerosis that occur. But that is occurring also in the cancer field.

You mentioned early detection of cancer, and that is one of, I think, the immediate applications of the discovery of changes in genes that contribute to a cell becoming cancerous; so that can lead to early diagnosis, much less expensive therapy and avoiding the very expensive cost of metastatic disease and, in addition, all of the suffering that occurs associated with that.

Mr. MILLER. You all do basic research, right? You all are all basic researchers?

Dr. NATHANS. Dr. Thomas does clinical research.

Dr. THOMAS. Some of both, but primarily clinical.

RESEARCH AND THE ROLE OF THE PRIVATE SECTOR

Mr. MILLER. Okay. My question is along the lines of going from basic to clinical to applied, and the role of the private sector.

Primarily, NIH is involved in funding on the extramural level basic research; is that correct? Dr. Varmus is shaking his head.

Dr. NATHANS. We are all having trouble, I think, because the line between basic and applied research is so blurred these days. We find people, who thought they were interested in fundamental research, who discover a gene and then get very much interested in finding out what that gene can be applied to in regard to health problems, and they establish a biotechnology company. That is what is driving the biotechnology industry, I think. It is really based on discovery supported primarily by NIH funds that leads to these new opportunities.

Mr. MILLER. Are there problems with the development of the private sector taking off on the applied areas?

Dr. NATHANS. I will bet, if you asked the Chief Executive Officers of all of the pharmaceutical and biotechnology companies in this country, they would tell you that what is happening to their companies is based to a great extent on federally supported research at universities.

Mr. MILLER. But don't they spend, far more on research than NIH?

Dr. NATHANS. No, no. I am saying it is based on the fundamental discoveries. They spend it primarily on development, not the kind of research that goes on at NIH.

Mr. MILLER. Is our system working well, do you think, the relationship between the private sector and government?

Dr. NATHANS. I think it is the envy of the world. In the pharmaceutical and biotechnology industry, I think it is the envy of the world.

Mr. MILLER. We are the leader in the world?

Dr. NATHANS. We are indeed.

Mr. MILLER. Where does the rest of the world fit in as far as up-and-comers?

Dr. NATHANS. I don't want to pose as an expert again, but it is clear that other areas of the world have recognized this as a growth area; and I think there are major investments now in biotechnology in Europe and in Japan.

Mr. MILLER. You can justify NIH just from the economics and the job creation as a world leader in this area. So it is more than just the basic research. I think you can expand the justification for a lot of this, because we are the leader in this area.

But is there a problem with the private sector going into the ethics issue? Are there potential problems ahead in the private sector as, the growth in NIH funding slows? It is going to be a struggle every year to get more money. We were successful this past year, but it is not going to grow as fast as maybe the demand is and the need. And so the private sector is taking on a larger portion of that.

Do you see any problems five years down the road along that way?

Dr. THOMAS. You know, the pharmaceutical companies certainly spend a great deal of money for research, and somewhere, I think in Dr. Varmus' testimony, there was some breakdown on that.

The trouble with that research is that it is directed really at the bottom line. If a disease is of sufficient frequency and if there is a reasonable chance of developing a drug that would be saleable,

they will devote a lot of money to it. But they are not going to do that for very basic research, and they are not going to do it for some of the rare diseases that we are interested in because of their fundamental significance, but we can't sell that to the pharmaceutical companies as being profitable sometime in the next few years.

Mr. MILLER. Well, thank you very much.

I will turn the questions over to Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman.

So many questions. It is always a great day for us when we are privileged to have the benefit of your thinking. Congratulations on your accomplishments and the recognition that you have received. So it is always—the time always seems to go faster when we have great minds to ask questions of, so I am going to go a little bit fast with my questions, if you don't mind.

BREAST CANCER

I was interested in hearing the conversation about directed and basic research, and I remember Dr. Varmus, before he was the Director, coming to my office and giving his pitch about the worms research, over and over again, I remember. I had two questions in that regard.

One is that last year when we had this wise person's panel, one of the questions that was asked about, was in my community, there is a large incidence of breast cancer—huge. It is a terrible competition, but right now The Bay Area seems to have a higher rate than in any other part of the country or indeed maybe in the world.

I was asking Dr. Bishop and other laureates who were gathered here where the answer might be, would it be in the laboratory or is it in the environment? And Dr. Bishop, far be it for me to characterize the answer of a Nobel Laureate, but it was my impression that he said the answer was in the laboratory.

When I took this back to our breast cancer seminar that we had later in the district, women were up in arms, because they believed that more should be done in terms of the surrounding communities, and environmental factors.

But I wonder if you could, in light of the information that I received from the women at the seminar, shed some light on where the answer might be to why one geographical area might have a higher incidence should we be studying the carcinogens or should we be working in the laboratory about how cancer develops. Knowing that in this room we have experts—what is the word—"beyond experts" in this field, I would hope that you could shed some light on this.

Dr. WIESCHAUS. It seems to me that the reason why one area might have a higher frequency of breast cancer might be due to environmental causes. But, if you change the question around to say, what is the most practical way of addressing this problem, then it seems to me that since we know that, in large part, environmental effects are causing alterations in gene activities—and ultimately that is what happens in tumors—from a practical standpoint to be able to develop treatments and to be able to develop cures, even if the local incidence is due to higher environmental causes, the practical solution is going to be to understand the genetics and under-

stand the cell biology. That, in my view, is what is really ultimately going to yield practical information, cures, diagnostics, ways of making life better for people in this area.

Ms. PELOSI. I understand you are talking about yielding cures, but—

Dr. WIESCHAUS. Or treatments.

Ms. PELOSI. And that is good, but what we are trying to do is prevent as well. I just wonder if you are talking about if, for the finite amount of money, as you said earlier, where the dollars are best spent in the laboratory on basic science, but if we could be on the dual track, is there any other worthwhile track to go down?

Dr. WIESCHAUS. Dual tracks are always better than the single tracks. I think you have to worry about your environment, but again, it is a calculation that you have to make, and I would always argue that you are better off understanding the real cellular basis for these diseases. It is going to be very hard to eliminate all of the environmental causes of cancer, although for the really obvious one, smoking, it makes sense to do that within our power. But I think the real power is going to be understanding the role of genes and understanding how these genes function within the cells.

Ms. PELOSI. Dr. Nathans, you talked about leukemia—excuse me, Doctor. Did you want to shed some light on that?

Dr. NATHANS. Could I just make a comment?

Ms. PELOSI. Mr. Chairman, the split second you opened that door I began my questioning. Is that not true, my colleagues?

Mr. MILLER. That is right.

Mr. PORTER. That is not only true, but we are under the 17-minute rule anyway.

Dr. NATHANS. I am sorry, am I eating into your time?

Ms. PELOSI. No, no, please, I hope you will.

Dr. NATHANS. I think one was to keep an open mind about environmental factors in any form of cancer. We know there are carcinogens in the environment. It is a very difficult area of investigation, in my opinion. It is basically an epidemiological type of investigation to try to pinpoint what it is of the millions of things that are in our environment, many of which are known to be carcinogenic under certain animal testing procedures, and it is often very difficult to pinpoint. So I certainly would think it is worth sifting through the evidence to see if you can develop some particularly suspect chemical or group of chemicals and then try to investigate that.

On the other hand, we know there are advances being made in the genetics of breast cancer, the discovery very recently of two genes that are involved at least in some forms of breast cancer. So it makes sense to pursue that discovery or those series of discoveries to try to find out what they mean and what one can make out of it diagnostically and therapeutically in the way of prevention, particularly early diagnosis. But, I mean, I think we need to keep an open mind as to what effect environmental carcinogens may be playing.

Ms. PELOSI. Thank you, Doctor.

Dr. THOMAS. I think the broad answer to your question is that we must proceed on all fronts. We need more basic knowledge; we need more knowledge of epidemiology. You may know that my in-

stitution is the recipient of a large grant for epidemiologic studies of breast cancer. This may not have helped the woman who has breast cancer today. So we have to be concentrating also on improvements in therapy, which gets me back to the autochthonous marrow transplant for breast cancer, which has been so obstructed by the insurance companies and the HMOs, where we need help in making it possible to do randomized prospective studies both of prevention and of treatment.

Ms. PELOSI. I appreciate that. Thank you.

Dr. Nathans, I didn't want you to get the impression in any way that I would diminish any resources going to the laboratory; I was just asking about conditionality, not any substitutions.

LEUKEMIA

Dr. Thomas, I wanted to go down a path with you that you took us down talking about leukemia and talking about a time when we might not need a transplant. I want to just read a sentence from our report language last year—well, it is supposed to be from last year, but we actually have only had this bill for a matter of weeks now.

"The committee recognizes the importance of continued research and clinical trials for leukemia. Noting that changes in health care financing have slowed the development of more effective treatment for leukemia, the committee urges the NCI to support further leukemia-related translational research for innovative, peer-reviewed clinical trials."

Is that language sufficient to the hope that you held out to us there? Would you suggest something stronger for this year's report language? I guess the critical words are "translational research for innovative peer review."

Dr. THOMAS. I suppose, as a brief summary, that perhaps that is the best we can do, but translational research, of course, ranges all the way from direct clinical trials of existing therapy to, for example, assessment of the significance of some of these chromosomal translocations in leukemia to more fundamental studies of just how these translocations result in abnormal cell behavior. So there are many levels to that question.

I guess that statement covers all levels, doesn't it?

Ms. PELOSI. It does, and I guess in the interest of saying it all, being comprehensive—I just wanted to make sure it did not exclude anything, but you are saying it is not specific enough?

Dr. THOMAS. No, I don't think it excludes anything.

STUDY OF ETHICS IN UNIVERSITY CURRICULA

Ms. PELOSI. And then you mentioned the word "ethics." Well, you were talking about third-party coverage of some of the clinical—well, all of you have addressed that. Do you think that we are doing enough in the curriculums of our universities in the ethics arena to be able to cope with what you are producing in the laboratories?

Certainly, I think it is an ethical question that third-party insurance coverers, if that is the correct terminology, understand that if you have the potential to help cure someone and they are the insurer of record of that person, then it shouldn't be an exercise in

pauperizing that family in order for them to access that care—Members of Congress, I am sure, and I get many, many calls of this kind from people about the choice they have to make in their families' lives.

I guess a question and a message to you: That is, as the example of excellence that we have in our country and the knowledge that you have, know thy power, in terms of getting more money for research, but also for elevating these kinds of ethical issues, whether it is ethical in the laboratory or in what kind of research we do, but also ethical in terms of how we make the blessings that you unlock available to people in a way that is in keeping with what we think we are investing in. Do you think that our universities, et cetera, while they are training scientists and researchers and all the rest, are doing enough on the liberal arts end not—to separate them out, but across the board?

Dr. WIESCHAUS. One of the things that we have instituted at Princeton over the past three or four years in our graduate program in molecular biology is that after the first two years, after the students have taken their science courses and then are basically qualified to do research, they still have—we still have a requirement in the third year; to take, as their only course, a course in ethics. It goes through ethical, social conduct as scientists, but also broadly into how our research affects social issues, diagnosis and other issues like that. The course is team-taught by someone in our department, but also someone in the ethics and philosophy department, to ensure that the course is broad and does address broad issues. I think that it has been a very valuable contribution to our graduate program.

Ms. PELOSI. Well, I am very pleased to hear that. I just hope they have it in the business school and the law school and the rest, because I think that is where—that certainly is essential where you are, because you are in new territory; but in terms of the general attitude about what is important and what our responsibilities are, I think we have to have it across the board.

SUPPORT FOR YOUNG SCIENTISTS

I agree with you that we have to have public policy which gives some confidence to young people that if they go into this field, that there is a future and that there will be opportunity.

What is the competition that you have for brilliant scientists that you would like to have, apart from another university? I mean, you can be a basic biomedical researcher, or they will go into the private sector or—

Dr. WIESCHAUS. The law school.

Ms. PELOSI. They go into other fields.

Dr. WIESCHAUS. Other fields. It is amazing. One of my students is completing law school now after having a Ph.D., and it is actually going to be a very useful thing because we have a molecular biologist who is also a lawyer. I also, though, had a graduate student 8 years ago who did really brilliant work, who went off and did postdoctoral work, had difficulties getting funding, and is now setting up a construction company.

Ms. PELOSI. And you thought this was a person who had great promise?

Dr. WIESCHAUS. Absolutely, one of the most promising students I had. But after a while, you get frustrated. You have your own life to live. You can't go through the constant struggle of trying to get funding, trying to do your research and not feeling it is supported.

Ms. PELOSI. Well, again I say, know thy power, because whether it is trying to affect public policy in relationship to insurance coverage for clinical—whether that is called treatment or experimentation, whatever it is, it is a potential assist to that particular family—or whether it is injecting a level of certainty into funding of grants that young people will have access to, because certainly any one of those young people could be an answer with the brilliance that they have been blessed with—is my time up, Mr. Chairman? How am I doing?

Mr. PORTER. Yes. Well, I will tell you what. We will go to Mr. Obey, because he has another event to attend, and then we will come back.

Ms. PELOSI. Thank you, Mr. Chairman.

Mr. PORTER. Mr. Obey.

Mr. OBEY. Thank you, Mr. Chairman.

Following up on Ms. Pelosi's question, I understand that there is quite a bit of tension between your field and the field of literature as well.

BUDGET DECISIONS AND FUNDING FOR BIOMEDICAL RESEARCH

Let me just say that I have sat on this subcommittee for over 22 years, and I guess that the most striking change in the testimony that we have heard over that time has been the testimony that we received on the NIH portion of the budget each year. One constant remains, which is, this subcommittee always places biomedical research at the top of its priority list. But one cannot help but to be struck by the totally different nature of the discussion in comparison to 20 years ago. We have really seen several revolutions since I first joined the subcommittee.

I guess I don't have any question; I guess I would just have a message, part of which was touched on by Ms. Pelosi. I have talked this year to probably 10 or 15 different scientific groups that have come to Washington to hold their meetings, and they will all ask us how they can get the Congress to understand the value of biomedical research; and I tell all of them and I guess I would especially tell you that I don't think that is a problem. I think that generally, across the board, there is very wide recognition of the value of putting our dollars into NIH and other associated programs.

I think the real challenge lies in the context of those budget proceedings. I think what needs to be understood is whether you look at President Clinton's budget or whether you look at Mr. Gingrich's preferred budget, you see in both areas determination to balance the budget over seven years. That means, under the kindest prescriptions, that there will be an immense reduction in the purchasing power of dollars appropriated to the domestic, discretionary portion of the budget, which is where we find NIH. You are talking reductions of at least 20 to 30 percent in real terms.

So it seems to me that the real question is not whether biomedical research should receive high priority within those decisions; it always will. The real question becomes how support for

any program can be sustained over the long haul, given those kinds of macroeconomic budget and fiscal decisions.

One example is that this year the budget resolution which we will be asked to support will contain a recommendation that will spend \$12 billion or \$13 billion more than the White House has requested for the military budget. You have strong forces in this Congress who are hell-bent to keep us appropriating \$260 billion a year to guarantee that we can sustain a two-and-a-half war strategy globally at the same time that we have a country that is extremely reluctant to send its soldiers anywhere. But we are going to spend a lot of money keeping them ready.

If we are asked to move \$12 billion in additional resources into the Pentagon this year, that will be \$12 billion of additional squeeze that will fall on this subcommittee, on housing, on environmental preservation and all the rest.

We also have an almost insatiable demand in this country to provide additional tax reductions to people who are already very well off, and it just seems to me that, in the end, if those who are interested in biomedical research want to sustain a high level of political support for those programs, they need to get involved in broader debate about our overall national priorities and our overall intentions in terms of the revenue base of our country. Because everybody—well, probably not everybody, but I have to say whether you talk to the most conservative Members of this Congress or the most liberal, you will find Members who will invariably say that they are strongly supportive of biomedical research, and yet some of the macroeconomic decisions this Congress makes will, over time, make it impossible to sustain the kind of financial support for biomedical research that we need.

You couldn't have a better friend in John Porter. I know that he feels that biomedical research has to stay at the top of the priority list. I don't know of anybody on this subcommittee who disagrees. But I think we all have to ask ourselves whether or not—even with that set of values that we all share, whether or not it is going to be possible to do that in the context of budget decisions which are saying that we will be cutting education over seven years by 20, to 30 percent; and manpower training, by 30 to 40 percent over that period of time. Sooner or later, even the most favored programs will feel an even greater squeeze than they have in the past.

So I think it is important that when scientists come to Washington, as a number of other groups did last week, that they remember the same thing that I asked other groups to remember, that in the end, if we can't get a better set of decisions at the macro level on the question of resource allocation, that it will sooner or later in the cycle be beyond the ability of this subcommittee to sustain the kind of funding that has been provided in the past.

Since I have been on this committee, we have seen funding for NIH go from around \$2 billion to almost \$13 billion today, and I would like to see that continue. But we really do need to have groups like yours to help this country understand that even the best of programs in the long term are going to be squeezed if we don't have a more rational set of decisions on both taxes and spending priorities than we are likely to get without that concerted effort.

BIOMEDICAL RESEARCH AND THE LAW

So basically that is the only message I have, except to follow up on what Nancy has said and also ask that you help make this Congress become much more aware than it is today of the need to help the state of the law catch up with the state of the science, especially in the area of genetics. Because if you take the example of the Kennedy-Kassebaum bill, that is virtually an afterthought, the problem was modestly recognized. We need to have a lot more actions taken by this Congress than have been taken to date if we are to assure that people, in the end, on balance, are more greatly benefited than they are harmed by the kind of knowledge which is becoming available. And if we don't have some rapid advances in the state of the law, I think in the end that balance is not going to turn out to be very pretty for people who we would like to think would be beneficiaries of the knowledge that people like you and your colleagues are helping this society to develop.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Obey. I don't have any basic disagreement with your message, actually.

Ms. Pelosi, why don't you take another minute or two and then we will have a second round of maybe five minutes each.

Ms. PELOSI. Thank you, Mr. Chairman.

Mr. PORTER. You had a little more time.

Ms. PELOSI. Thank you, Mr. Chairman.

BUDGET PRIORITIES

I am fond of saying of this committee that the power that we have is almost biblical, because we can put the resources to the path of opportunity that has been described here to, hopefully, produce a cure; and I agree with what Mr. Obey was saying about the state of the law. Obviously we are going along that path, but I believe if we see opportunity, we have a moral obligation to provide the resources to produce such a cure.

I also believe, as I said, that if clinical work that you do—could help people, that a third party should be paying for them. I wanted to just take that to another step.

Just one thought that Mr. Obey said about sooner or later the cutting-edge patient and the rest, I don't think that helps defense or basic biomedical research, because we have to have fresh recruits in both arenas over time. But I do want to dwell for a moment on Mr. Obey's budget priorities—the budget priorities that he talked about.

Many of us have talked for a long time about the idea that we put so much of our resources and our creative energies to the most destructive means, rather than the more beneficial means. Certainly we have to have a strong national defense, but while we boast about and salute our Chairman, and rightfully so, for his leadership in having a good figure for NIH for research. However, it is important to remember that research in the Air Force probably exceeds the research for NIH this year—and NASA, and the list goes on and on.

The House budget resolution that is being presented for 1997 for NIH "freezes the NIH research at last year's level of \$11.9 billion

and continues funding at this level through 2002." This represents a decline in real purchasing power of 15.9 percent by 2002, just to quantify some of what Mr. Obey was saying.

So I wondered if you could just speak to the issue of the trend more to increasing defense R&D and freezing the research figure for the NIH, because Mr. Obey's statement is quite correct.

As I say, our Chairman is not a party to putting up walls where you can't take money from defense and bring it over to domestic programs, and he is not a party to saying we should cut or freeze NIH and have a tax break for certain individuals in our society who live perfectly well without them. So I feel very comfortable presenting this question to you, not that I wouldn't do it anyway, but I say that recognizing the suggestion in this budget is not—I don't associate our Chairman with that.

Could you comment on that?

Dr. THOMAS. I will try to comment on it.

First of all, I would like to thank Mr. Porter and the members of this committee for the budget that we had this year. I think many of us were concerned that it would be much worse, and we appreciate that very much.

Ms. PELOSI. I am glad you like it, Doctor, because we are going to have it until the year 2002.

Dr. THOMAS. In regard to the macro budget problem, obviously that is beyond our purview, as it is yours, but we can certainly write letters and try. As long as the military budget is fixed and social security is fixed and welfare is fixed, and aid to tobacco farmers is fixed, and the gas tax has to be repealed, I am not sure where we can start, except that I get back, as I mentioned, to looking at our children and grandchildren. I think they will be the recipients of these advances in biomedical research that we have been talking about, and we ought to do everything possible to look at their welfare.

Ms. PELOSI. Thank you, Doctor.

Dr. Nathans.

NEED INVESTMENT IN RESEARCH FOR THE FUTURE

Dr. NATHANS. I think biomedical research is one of those areas where, happily, the benefits to the health and welfare of the American people, the direct benefits, are more or less equaled by the economic benefits to the country. It seems to me that that ought to be factored in. This is all quite aside from this question of balance between investment in the future and investment in current problems.

Clearly, we do need to invest in the future, and I think if the NIH budget in real dollars is level, as you suggest, between now and 2002 that we are going to find it impossible to support the kind of research enterprise that I think the American people basically want, and that makes sense. I think we will be losing young people; that will be the most devastating thing, because they will see the opportunities are not there, and there will be lots of promising leads which are now in this very rapid period of advance for medical science—they are just enormous—they will fall by the wayside. And I think there will be economic fallout for our biomedical

research industries. So I don't know where—I am not suggesting, I know where the money is going to come from.

You may know that Johns Hopkins University has an applied physics laboratory which does research primarily for the Navy, but also for other branches of the Defense Department and the government; and it seems to me, and listening to the discussion that I first learned about when I was a member of President Bush's Council on Science Advisors—Science and Technology Advisors—that there has to be an investment in advanced military technology for the security of the country, but we have to come to grips with trying to contain the Defense Department budget to reasonable levels.

Ms. PELOSI. Thank you.

Dr. Wieschaus.

Dr. WIESCHAUS. I would just like to say, that with a 15 percent cut in real terms, I think that the most immediate consequence of that will be on younger scientists. Because it is just very difficult to protect them or to fund original ideas or young people under situations where money is really, really very short and you are cutting back 15 percent.

So the scary thing about that is that it is the young people, and I am the youngest person sitting at this table, but I am talking about people who are 15 years younger than I am. It is those people who are not going to be funded and those people who have the ideas and those people who are going to discover the things that are going to be important in the year 2010. Those are the people who are going to be hurt by such a cut, and the Nation is going to be hurt.

Ms. PELOSI. Thank you. Thank you, gentlemen.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi. We will try an abbreviated third round here. I have one question for each of you.

HUMAN EMBRYO RESEARCH

Dr. Wieschaus, Congress this past year prohibited any funding for NIH to conduct human embryo research of any type. In your opinion, is this the right thing to do, and if there were funds available, what type of research would you see as being important in this area?

Dr. WIESCHAUS. I don't think it was the right thing to do. My own personal view on this, on the issue, and a view that has developed in part because I have lived my life as a scientist looking at embryos, is that embryonic development is a gradual process and that in the very early stages of development, a fertilized egg is much more similar to an unfertilized egg than it is to a developed human baby. And for those reasons it seems to me that that decision puts an inordinate worth or value on the fertilized egg versus the potential great value of understanding certain processes and understanding the effects and understanding other issues of clinical importance. So that is my personal view, and it is a view that is based on my development as a scientist.

I think what I am saying is that you can reverse it and say that it is hard to come up with a scientific justification for that view. I realize many people whom I respect a great deal might have

other views of a fertilized egg, but it is a view that I think is based on strongly held religious beliefs, and those have great value. But they are our religious beliefs, and it is not a view that is based on any scientific predictability.

Mr. PORTER. Thank you.

MARROW TRANSPLANTS

Dr. Thomas, in 1990 you received the Nobel Prize for work and discoveries in bone marrow transplantation. We have been talking in our subcommittee and in testimony from NIH directors about umbilical cord stem cell transplants just six years later, and I think you say in your written testimony and referred to it in your oral testimony, that there has been a lot of progress in this new area.

Are we producing change at a revolutionary pace here? Is this unusual? What is your reaction to the speed at which things seem to be moving in this particular area?

Dr. THOMAS. Well, there has been a lot of progress, and I think the speed with which it is moving is commendable.

You know, when we talked about marrow transplantation, we really talked about the seed cells that are contained in the marrow that have the ability to grow up and repopulate the marrow all over again. And we found in 1962, in the dog, that we could actually get marrow grafts with peripheral blood cells from the circulating blood, but we didn't pursue that because the technology was so cumbersome then.

Now we are seeing a rapid shift, because we have continuous flowcentrifuges that can separate cells from the blood; and we have recombinant growth factors that stimulate the release of these seed cells into the circulating blood. So in the next year or two, I think we will no longer be talking about marrow transplantation, we will be talking about transplantation of seed cells obtained from the peripheral blood.

CORD STEM CELL TRANSPLANTS

Now, the cord blood is a new development. It was recognized by Hal Broymeyer in Indiana that the cord blood had a lot of these seed cells in it; and the first transplant with those seed cells from the cord blood was done by Dr. Ilian Gluckman in Paris, who trained with us a number of years ago.

Now, there is a lot of interest in a bank of cord blood cells because the cord and the placenta are ordinarily discarded after the baby is delivered; and at the New York Blood Center now and several other centers, including ours, there are banks being set up with tissue types that can be frozen, that can be kept indefinitely, and already more than 100 transplants have been done in this country using cord blood cells.

Now, this gets us into a number of ethical and practical problems. Who owns these cells? Is it the mother, is it the newborn baby? And what safeguards can we put into effect to be sure that these cells don't carry a disease like AIDS or hepatitis or something. Actually, there are two societies in the United States that have been addressing this issue in some detail, including the ethical issues involved. It is rapidly evolving, and yet it offers the op-

portunity of taking the product which is ordinarily discarded and making it very useful to patients who are in need of stem cell transplant.

Mr. PORTER. Thank you Dr. Thomas.

TUMOR VIRUSES

Dr. Nathans, in your testimony you mention that you—and this was apparently some time ago—you went to the Weizman Institute in Israel to study tumor viruses. I wonder if you could give us kind of an overview. We like to think of ourselves as leading the world in everything, but obviously there are areas where we have colleagues around the world who have a great deal of expertise as well. Could you give us an overview of biomedical research and where it is concentrated and where it has done well?

Dr. NATHANS. You don't have to worry about the standing of the United States. I think it is at the top. But there are excellent people not in the United States. Dr. Weischaus mentioned his colleague who is in Germany. I went to the Weizman Institute because there were two people there named Leo Sachs and Ernst Winocur, particularly Ernst Winocur, who was doing exciting work in tumor viruses. I went there to learn about tumor viruses. It was also an interesting time for my children to be in Israel and to visit the ancient sites there and learn about the culture there.

Mr. PORTER. What year was that?

Dr. NATHANS. This was in 1969.

So during a six-month sabbatical I learned a great deal about tumor viruses and about restriction enzymes and began to put the two together and planned out a series of experiments for when I got back.

It was a very fruitful time, and a sizable number of Americans still go abroad as postdoctoral fellows to work in outstanding laboratories in Europe, Japan or Great Britain, and I don't think it means that we have lost any of our preeminence in biomedical science. But science is an international activity, and many of us collaborate with scientists from different parts of the world. It is easier to do now because of telecommunications. So it is an international effort. It never occurred to me that this was leaving the country, so to speak, to do science.

Mr. PORTER. Mr. Miller.

EFFICIENT USE OF RESOURCES

Mr. MILLER. We have some tough choices here. We have only so much money available. Of course, biomedical research rates very high with us, but this is the same amount of money that Head Start comes out of and job training programs and such. I think NIH funding will continue certainly, not flat; hopefully it can go up. The question is how can we make better use of the money.

On the issue of regulations, you mentioned animal research problems. What can we do from either a regulatory or bureaucracy standpoint to make more efficient and better use of the funds that come out of NIH? Could we just anecdotally—are there some things that we should be able to do, not necessarily from this committee, FDA, Department of Agriculture, regulations and such; have you

had problems that the bureaucracy is causing you to waste resources, audit functions and such, or is that much of a problem?

Dr. NATHANS. I am thinking hard.

Mr. MILLER. Maybe it is not that much of a problem.

Dr. NATHANS. You know, there is a lot of auditing, and personally I think we need to do that. I think it is good to have to be accountable for expending public funds, so basically I can't object to it.

It takes a great deal of time and resources and money, speaking now as an administrator at the university, but we have to be accountable, so there may be ways to streamline that and make it less costly. A number of faculty members, of course, spend a lot of time writing grant applications because of the tightness of the funding at the present time, and recent past. So that is a great deal of time expended, I think.

There is, I think, fairly strict regulation of animal care, and maybe Dr. Thomas would know more about that than I. That again takes time and money to do. A certain amount of that is, I think, a good thing, in order to see that animals are used in a humane way.

So I can't say that I have major things on my mind in that regard about how we can make better use of the money. Maybe some of my colleagues have other thoughts about it.

ANIMAL RESEARCH

Mr. MILLER. I have heard complaints from people in particular about animals, the cost of maintaining and caring for them. I don't know how much of a problem that is.

Dr. THOMAS. My discussion of this was directed really at distinguishing what we need to do for the care and comfort of our animals as contrasted to what is done by the People for the Ethical Treatment of Animals people to be simply obstructive, and some of that is pushed through just to be obstructive. Certainly we want to do the humane thing for our animals.

Mr. MILLER. If you come up with ideas that you think we need to address in regulatory areas, let us know. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you.

Ms. Pelosi.

Ms. PELOSI. I want to follow up on Mr. Miller's comments about animal research; however, I am coming at it from a different direction. I am sympathetic to the additional cost and time that it takes to address the regulations relating to humane treatment of animals, but thoroughly support humane treatment of animals. On the other hand, I sympathize in terms of the need for animal research.

Mr. Chairman, have you been to San Francisco recently? It is a very big issue. Perhaps it is in your district as well. One of the reasons it is is because many of these people manipulate the media. When I had the media come in and say what are the main issues on Capitol Hill, one is humane treatment of animals, so they do a very job of showing up at every meeting, of asking a question all the time, of calling the stations and saying, you haven't shown enough stories about inhumane treatment of animals, et cetera.

I think, again stipulating that we all want to treat animals humanely and must go the extra mile to do that, people in my district say they have not found a cure for anything using animal research. If your child were sick and there was an answer that could be found using animal research, it doesn't matter; or would you like to go from the laboratory to humans, or let's stop on animals, other animals, they always say they would rather just go from laboratory per se, basic research to humans.

So we are not talking about a situation where we can persuade without information. I mean, the very idea that somebody would say they have never found a cure for anything testing animals anyway, and if they had, would that change your minds, maybe not. But just listening to you today talk about places where this has been beneficial I think is also beneficial in the debate.

So again, you have the information. I think it is very important to get it out there as well as to understand how mobilized they are. Our community, Dr. Varmus can tell you it is a way of life for certain people. While I am respectful of their views, we also cannot have paths of opportunity closed to us, not because they are going to prevent research with use of animals, because that must happen, but because certain opportunities may be foreclosed to us in certain regions of the country or circumstances, or just delay.

I again say you have the responsibility, because you have the knowledge that can be helpful to us in responding—and to other members in responding to this activism that is there, but I respect their right to have the view and draw the line from humane to no animal research, but call upon you to help us document successes that have occurred, and we know they have.

Once again, I do want to thank you for being so generous with your time here today, for my part. I know our Chairman wants to thank you. For my part, it has been a real privilege to listen to all of your answers, and I wish you much success in your pursuits. Doctor, while your father's research may have been pitiful with regard to where science was at the time, he did bless you with his genes, so we are benefiting from his good work and his gift to the rest of us.

Mr. PORTER. Thank you.

Let me thank you, Dr. Thomas, Dr. Nathans, Dr. Wieschaus. We have had a fascinating two hours and as always have learned a great deal. You have not only educated us, but given us a lot of insight as to the possibility of the science and the pace of discovery, and we very much appreciate your taking time from your busy schedules to be here and spend it with us. Thank you very much.

The subcommittee will stand in recess until 10 a.m. tomorrow.

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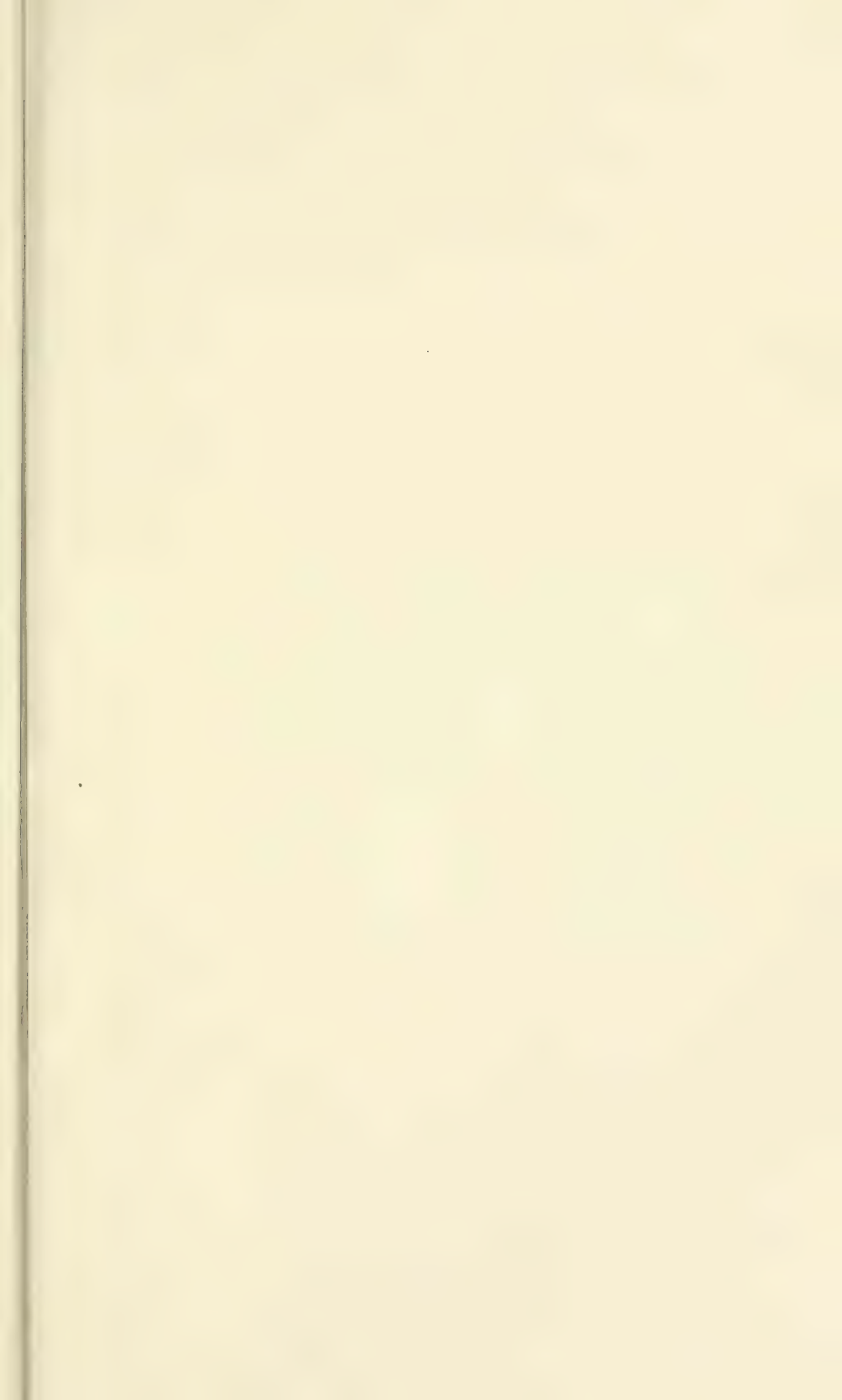
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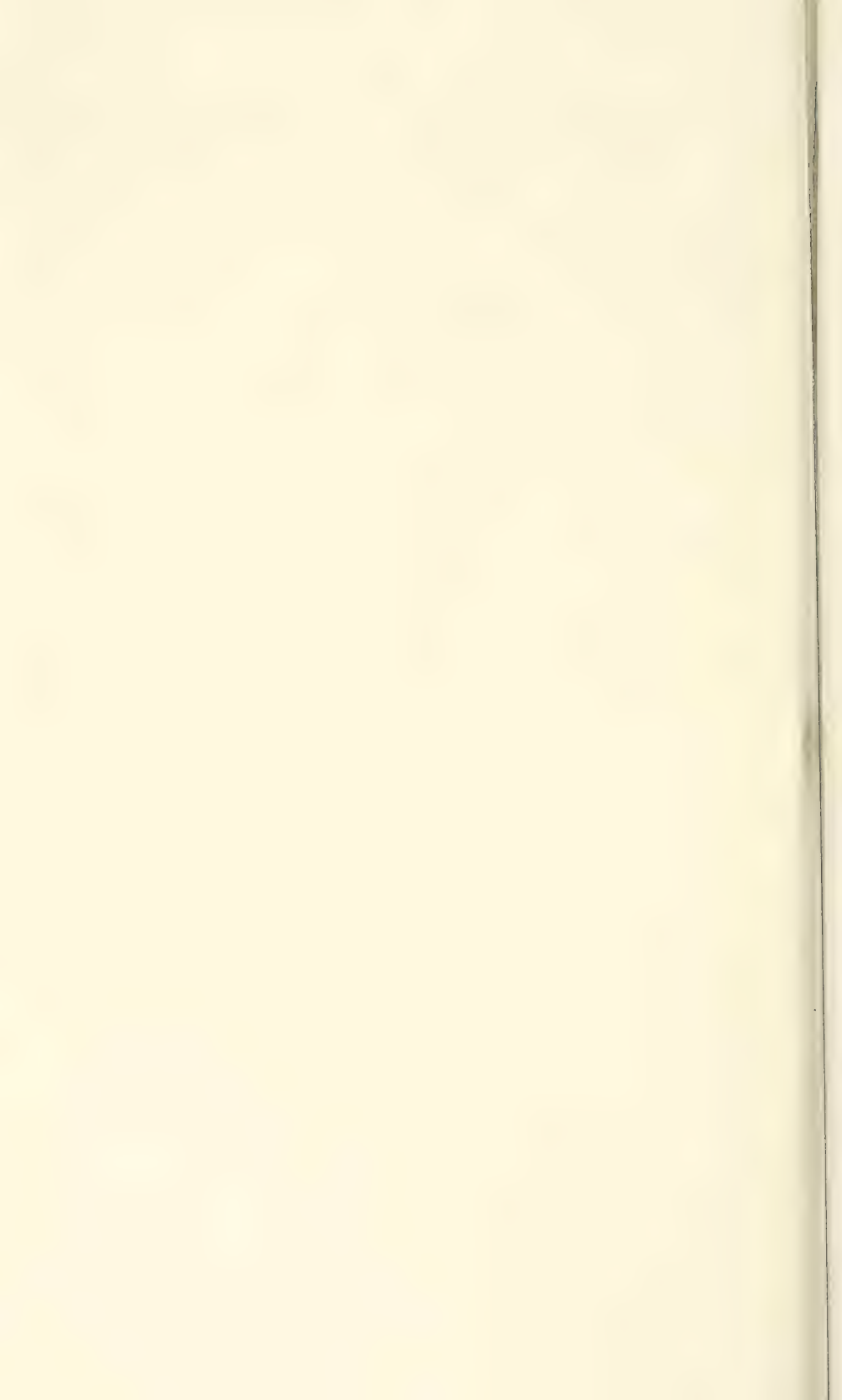
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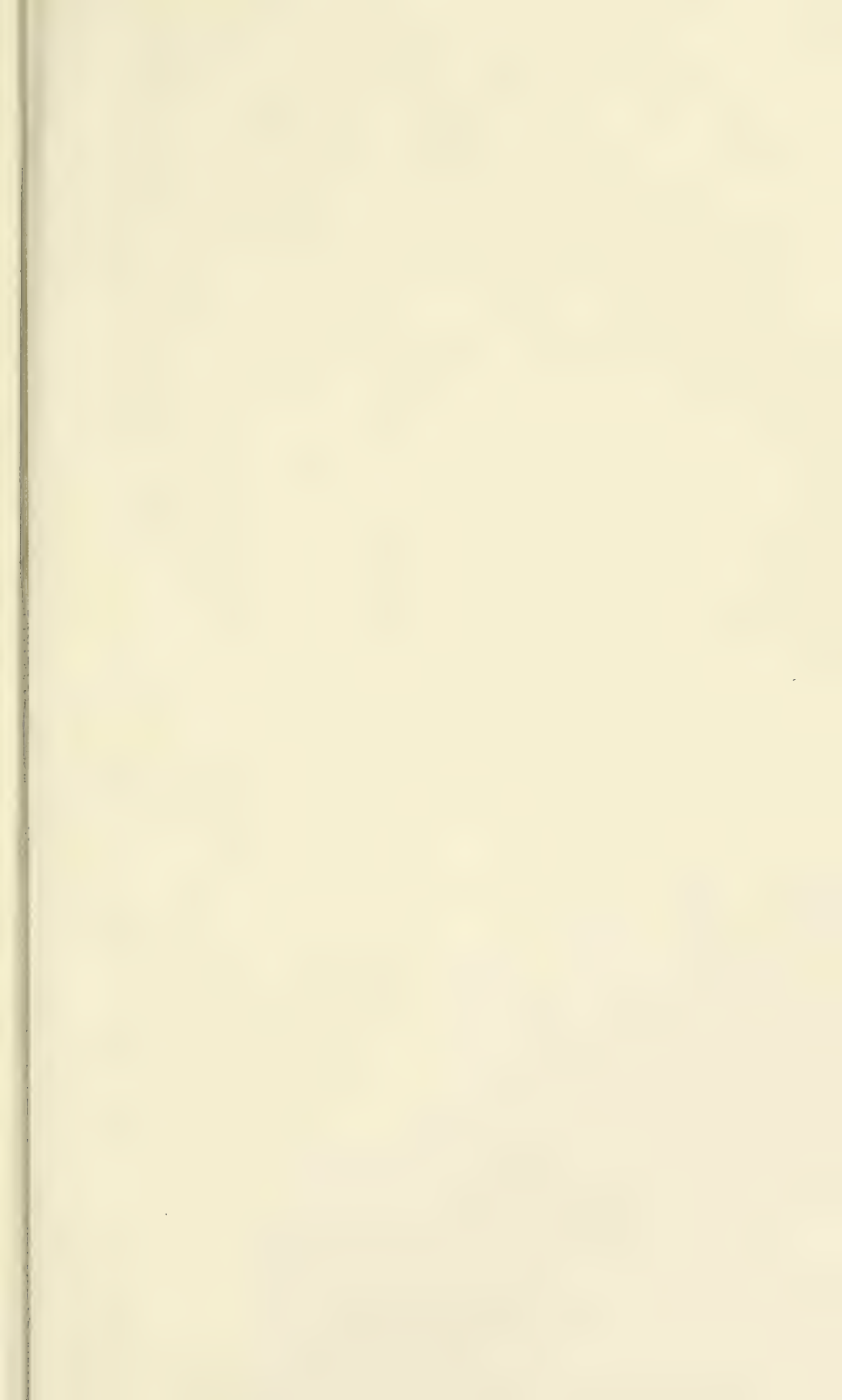
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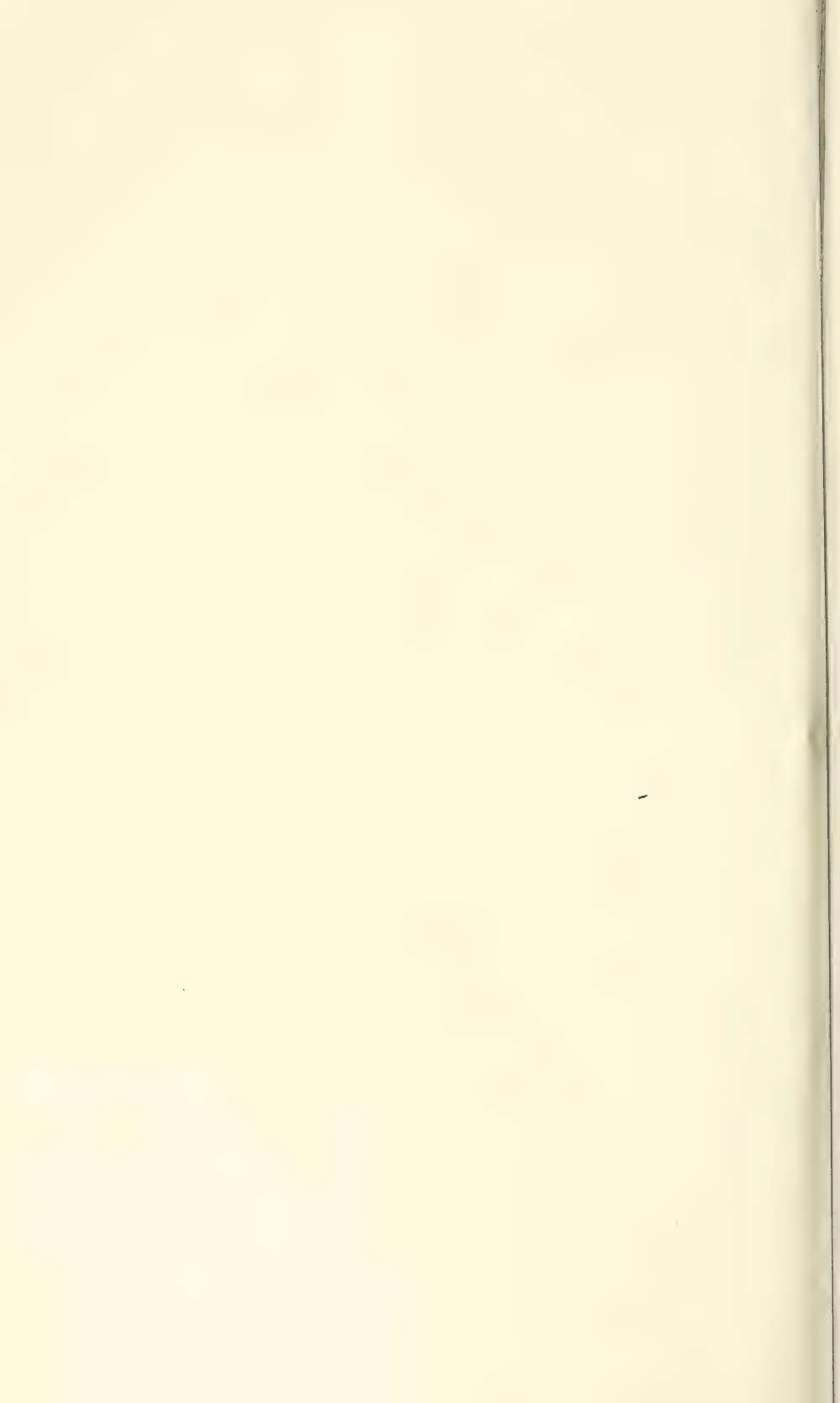


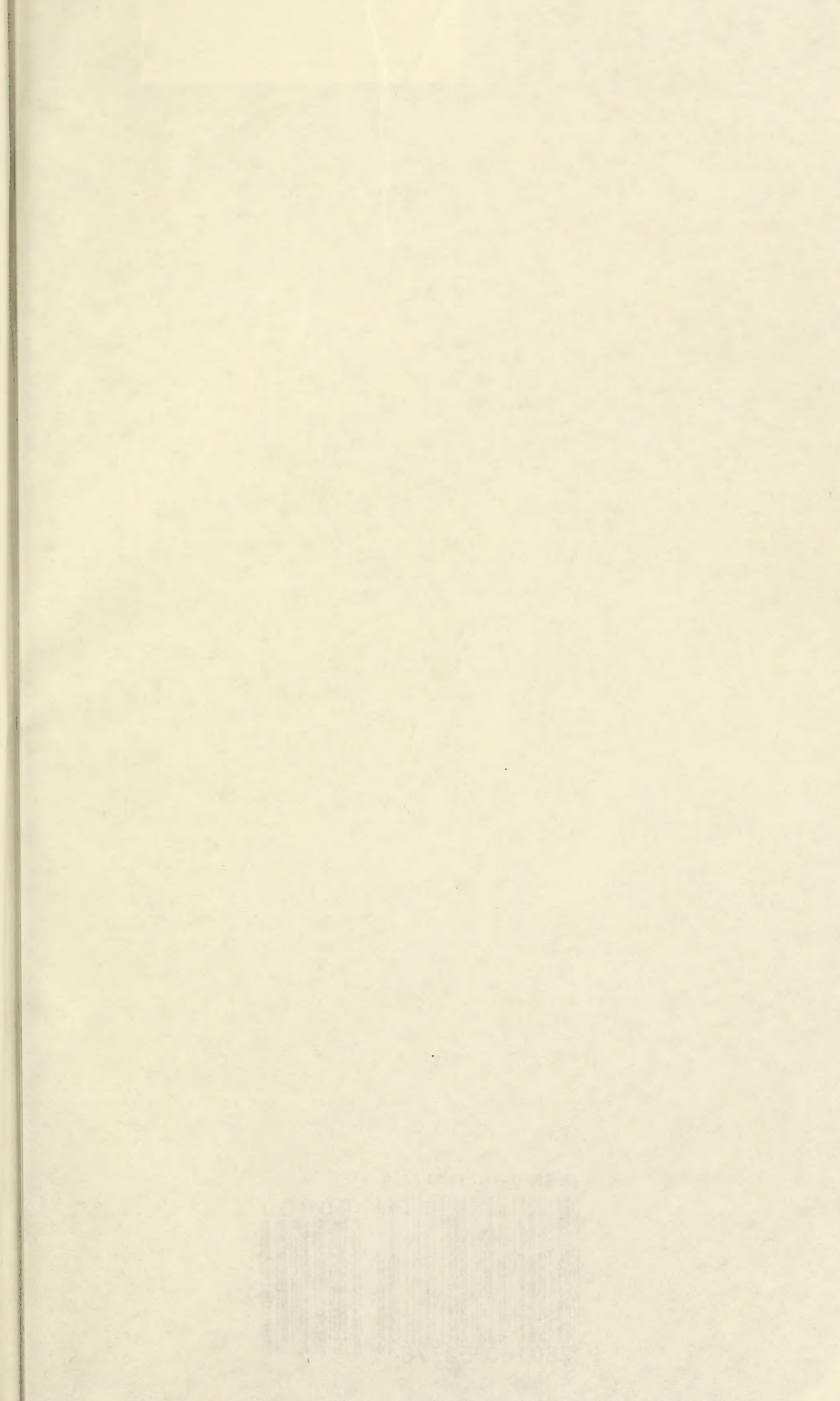












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